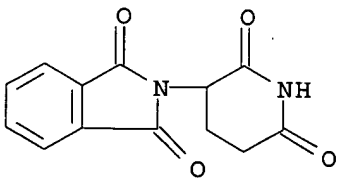
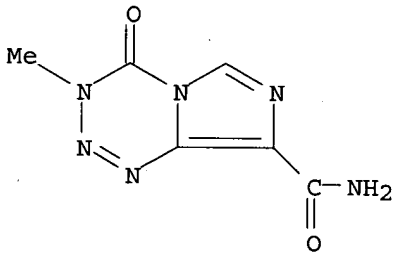
L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 50-35-1 REGISTRY
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phthalimide, N-(2,6-dioxo-3-piperidyl)- (6CI, 7CI, 8CI)
OTHER NAMES:
CN (.+-.)-Thalidomide
CN .alpha.-(N-Phthalimido)glutarimide
CN .alpha.-N-Phthalylglutaramide
CN .alpha.-Phthalimidoglutarimide
CN 1,3-Dioxo-2-(2,6-dioxopiperidin-3-yl)isoindoline
CN 3-Phthalimidoglutarimide
CN Celgene
CN Contergan
CN Distaval
CN K 17
CN Kevadon
CN N-(2,6-Dioxo-3-piperidyl)phthalimide
CN N-Phthaloylglutamimide
CN Neurosedyn
CN NSC 66847
CN Pantosediv
CN Quetimid
CN Sedalis
CN Sedoval
CN Softenil
CN Softenon
CN Suaramide
CN Talimol
CN Talinol
CN **Thalidomide**
CN Thalomid
FS 3D CONCORD
DR 14088-68-7, 731-40-8
MF C13 H10 N2 O4
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGNL, DRUGU, DRUGUPDATES, EMBASE, HODOC*, HSDB*, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PHAR, PHARMASEARCH, PIRA, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1274 REFERENCES IN FILE CA (1957 TO DATE)
68 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1278 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 85622-93-1 REGISTRY
CN Imidazo[5,1-d]-1,2,3,5-tetrazine-8-carboxamide, 3,4-dihydro-3-methyl-4-oxo- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN CCRG 81045
CN M and B 39831
CN MB 39831
CN Methazolastone
CN NSC 362856
CN Sch 52365
CN Temodal
CN **Temozolomide**
FS 3D CONCORD
DR 97716-75-1
MF C6 H6 N6 O2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PHARMASEARCH, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO



L8 ANSWER 1 OF 40 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:363934 BIOSIS
DOCUMENT NUMBER: PREV199900363934
TITLE: New chemotherapy options for the treatment of malignant gliomas.
AUTHOR(S): Burton, Eric (1); Prados, Michael
CORPORATE SOURCE: (1) Department of Neurosurgery M787, San Francisco, CA, 94143-0112 USA
SOURCE: Current Opinion in Oncology, May, 1999) Vol. 11, No. 3, pp. 157-161. ISSN: 1040-8746.
DOCUMENT TYPE: Article
LANGUAGE: English

L8 ANSWER 2 OF 40 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
ACCESSION NUMBER: 2000:32094859 BIOTECHNO
TITLE: A comparison of treatment results for recurrent malignant gliomas
AUTHOR: Nieder C.; Grosu A.L.; Molls M.
CORPORATE SOURCE: C. Nieder, Department of Radiation Oncology, Klinikum rechts der Isar, TU Munich, Ismaninger Str. 22, 81675 Munich, Germany.
SOURCE: Cancer Treatment Reviews, 2000), 26/6 (397-409), 62 reference(s) CODEN: CTREDJ ISSN: 0305-7372
DOCUMENT TYPE: Journal; General Review
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2000:32094859 BIOTECHNO
AB Retreatment of malignant gliomas may be performed with palliative intent after careful consideration of the risks and benefits, and with special regards to iatrogenic neurotoxicity and quality of life (QOL). This review compares studies of several retreatment strategies (published between 1987 and 2000) based on the quality of their evidence. Depending on both established prognostic factors and previous treatment, individually tailored retreatment strategies are possible. In all studies that included a multivariate analysis of prognostic factors, performance status was the most important. So far, predictive factors for response, which might facilitate patient selection, have not been unequivocally defined. In terms of QOL, single-agent chemotherapy (temozolomide, nitrosoureas, platinum and taxane derivatives) may offer a better therapeutic ratio than polychemotherapy. For glioblastoma multiforme, progression-free survival and QOL were more favourable after temozolomide than procarbazine (level I evidence). The survival of patients after various radiotherapy techniques is broadly similar. However, considerable toxicity is associated with radiosurgery or brachytherapy. Fractionated stereotactic radiotherapy plus radio-sensitizing cytostatic agents has shown promising initial results in small groups of selected patients and awaits further evaluation. Level 2 evidence derived from non-randomized studies does not suggest a substantial prolongation of survival by re-resection as compared with chemotherapy or radiotherapy alone. Level I evidence derived from a randomized trial suggests that application of BCNU polymers significantly improves the outcome after re-resection. However, most studies reported median survival in the range of only 25-35 weeks, thereby emphasizing the need for the development and clinical evaluation of new innovative treatment approaches. .COPYRGT. 2000 Harcourt Publishers Ltd.

L8 ANSWER 3 OF 40 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
ACCESSION NUMBER: 2000:30981156 BIOTECHNO
TITLE: Chemotherapy in malignant gliomas
AUTHOR: Burton G.V.
CORPORATE SOURCE: Dr. G.V. Burton, Feist-Weiller Cancer Center, LA State Univ. Health Science Center, 1501 Kings HW, Shreveport, LA 71130-3932, United States.
SOURCE: Seminars in Neurosurgery, 2000), 11/3 (373-385), 92 reference(s) CODEN: SNEEAH ISSN: 1526-8012
DOCUMENT TYPE: Journal; General Review
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2000:30981156 BIOTECHNO
AB Current chemotherapy approaches to patients with malignant gliomas have little impact on patient outcomes. Surgical and radiotherapy, although providing the majority of benefit, have little potential for significant further improvement of patient survival. Medical therapy, especially with expanding knowledge relative to tumor resistance, oncogenesis pathways, and angiogenesis, has great potential for altering the outcomes of patients with malignant gliomas. New cytotoxic agents such as temozolomide and CPT-11 appear to have significant activity; however, anti-angiogenesis therapy, gene therapies directed at oncogenic pathways, and immuno-toxin constructs may have the greatest potential. Only by participation in clinical trials can these new agents be developed to benefit future patients with malignant gliomas.

L8 ANSWER 4 OF 40 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
ACCESSION NUMBER: 2000:30744566 BIOTECHNO
TITLE: Drugs of choice for cancer chemotherapy
SOURCE: Medical Letter on Drugs and Therapeutics (18 SEP 2000, 42/1087-1088 (83-92) CODEN: MELEAP ISSN: 0025-732X
DOCUMENT TYPE: Journal; General Review
COUNTRY: United States
LANGUAGE: English
AN 2000:30744566 BIOTECHNO

L8 ANSWER 5 OF 40 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
ACCESSION NUMBER: 2000:30627466 BIOTECHNO
TITLE: Development of new antineoplastic agents with known and novel mechanisms of action
ENTWICKLUNG NEUER ANTINEOPLASTISCH WIRKSAMER SUBSTANZEN MIT BEKANNTEN UND NEUEN WIRKUNGSPRINZIPIEN
AUTHOR: Lipp H.-P.
CORPORATE SOURCE: Dr. H.-P. Lipp, Universitatsapotheke, Rontgenweg 9, 72076 Tubingen, Germany.
SOURCE: Krankenhauspharmazie, 2000), 21/8 (396-419), 136 reference(s) CODEN: KRANDZ ISSN: 0173-7597
DOCUMENT TYPE: Journal; Article
COUNTRY: Germany, Federal Republic of
LANGUAGE: English; German
SUMMARY LANGUAGE: English
AN 2000:30627466 BIOTECHNO
AB It is a great challenge to find new cytostatics with well-known mechanisms of action which will have (I) a greater therapeutic index, (II) an improved pharmacokinetic behaviour, (III) additional intracellularly located targets or (IV) increased activity against resistant cells. In this regard, examples like Oxaliplatin, TAS-103, CI-941, the Multitargeted Antifolate (MTA), Temozolomide or Eniluracil represent encouraging developments. In the meantime several inhibitors of farnesyl transferases, matrix metalloproteinases, telomerase or different kinases as well as antisense-oligonucleotides or tirapazamine are matter of clinical research. Additionally, substances like SDZ PSC 833 or Benzylguanine may help to overcome multi-resistant conditions.

L8 ANSWER 6 OF 40 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
ACCESSION NUMBER: 2000:30407535 BIOTECHNO
TITLE: A review of current and future treatment strategies for malignant astrocytomas in adults
AUTHOR: Nieder C.; Nestle U.
CORPORATE SOURCE: Dr. U. Nestle, Abteilung fur Strahlentherapie, Radiologische Universitatsklinik, D-66421 Homburg/Saar, Germany. E-mail: raunes@med-rz.uni-saarland.de
SOURCE: Strahlentherapie und Onkologie, 2000), 176/6 (251-258), 81 reference(s) CODEN: STONE4 ISSN: 0179-7158
DOCUMENT TYPE: Journal; General Review
COUNTRY: Germany, Federal Republic of
LANGUAGE: English
SUMMARY LANGUAGE: English; German
AN 2000:30407535 BIOTECHNO
AB Background: For more than 20 years, after establishing the role of postoperative radiotherapy for malignant astrocytomas, no definitive improvement in survival rates could be observed, despite advances in established treatment modalities such as radiotherapy and chemotherapy. This review discusses available laboratory and clinical data as well as recent advances in our knowledge about prognostic factors (Table 1) and their implications for the design of future clinical trials. Results: Elucidation of the biology of malignant astrocytomas allowed for development of rational new approaches, such as gene therapy and immunotherapy, which could interfere with established treatment regimens or being used independently. Possible strategies include the restoration of defective cancer-inhibitory genes, cell transduction or transfection with antisense DNA corresponding to genes coding for growth factors and their receptors, or with the so-called suicide genes. Several antiangiogenic approaches such as administration of thalidomide, protamine, or monoclonal antibodies against vascular endothelial growth factor have been developed, too. Further treatment possibilities include modulation of drug resistance, e.g. by P-glycoprotein antagonists or O6-alkyl-guanine-DNA-transferase inhibitors, inhibition of matrix metalloproteinases, inhibition of protein kinase C, and administration of agents such as phenylbutyrate or valproic acid that showed promising antiproliferative effects in vitro. Conclusions: Several rational new approaches are now entering clinical trials (Table 2). In the light of limited survival after standard treatment it is recommended that patients should be offered participation in such trials.

L8 ANSWER 7 OF 40 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
ACCESSION NUMBER: 2000:30175900 BIOTECHNO
TITLE: Chemotherapy for high-grade gliomas
AUTHOR: Galanis E.; Buckner J.
CORPORATE SOURCE: E. Galanis, Division of Medical Oncology, Mayo Clinic and Foundation, 200 First Street SW, Rochester, MN 55905, United States.
SOURCE: British Journal of Cancer, 2000), 82/8 (1371-1380), 117 reference(s) CODEN: BJCAAI ISSN: 0007-0920
DOCUMENT TYPE: Journal; General Review
COUNTRY: United Kingdom
LANGUAGE: English
AN 2000:30175900 BIOTECHNO

L8 ANSWER 8 OF 40 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
ACCESSION NUMBER: 1999:29297484 BIOTECHNO
TITLE: New treatment strategies for malignant gliomas
AUTHOR: Avgeropoulos N.G.; Batchelor T.T.
CORPORATE SOURCE: Dr. N.G. Avgeropoulos, Massachusetts General Hospital, Brain Tumor Center, 100 Blossom Street, Boston, MA 02114, United States. E-mail: batchelor@helix.mgh.harvard.edu
SOURCE: Oncologist, 1999), 4/3 (209-224), 126 reference(s) CODEN: OCOLF6 ISSN: 1083-7159
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1999:29297484 BIOTECHNO
AB Although survival in patients with malignant gliomas remains limited, there is renewed optimism with the emergence of novel treatment strategies. Cytotoxic agents such as temozolomide and CPT-11 have shown promising clinical activity. Biological treatments for brain tumors, including antisense oligonucleotides, gene therapy, and angiogenesis inhibitors, are also being evaluated in clinical trials. Delivery strategies have been developed to overcome challenges presented by the blood-brain barrier. These noteworthy treatments, alone or in combination, may ultimately prolong survival and enhance quality of life in this group of patients.

L8 ANSWER 9 OF 40 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
ACCESSION NUMBER: 1999:29090070 BIOTECHNO
TITLE: Innovative therapies for pediatric brain tumors
AUTHOR: Rubin J.B.; Kieran M.W.
CORPORATE SOURCE: Dr. J.B. Rubin, Dana Farber Cancer Institute, Department of Pediatric Oncology, 44 Binney Street, Boston, MA 02115, United States.
SOURCE: Current Opinion in Pediatrics, 1999), 11/1 (39-46), 143 reference(s) CODEN: COPEE0 ISSN: 1040-8703
DOCUMENT TYPE: Journal; General Review
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1999:29090070 BIOTECHNO
AB Success in the treatment of pediatric brain tumors has lagged behind that of other pediatric cancers. This paper highlights many of the advances that have taken place over the past few years in the surgical, radiotherapeutic, and chemotherapeutic approaches to central nervous system lesions that we hope will lead to a dramatic improvement in outcome. Innovations in neurosurgical and radiotherapeutic techniques have resulted in decreasing toxicity although substantial improvement in cure rates has not been observed. Many new techniques such as gene therapy, angiogenesis inhibitors, immunotherapy, and others that have not been part of the classic approach to these lesions are now in clinical trials in the hope that they will impact on the survival of these patients. The scientific basis for these new treatment modalities and preliminary clinical results are discussed.

L8 ANSWER 10 OF 40 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
ACCESSION NUMBER: 1998:28464352 BIOTECHNO
TITLE: New frontiers in therapy of malignant gliomas
AUTHOR: Puduvalli V.K.; Yung W.K.A.
CORPORATE SOURCE: W.K.A. Yung, Department of Neuro-oncology, The University of Texas, M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, United States.
SOURCE: FORUM - Trends in Experimental and Clinical Medicine, 1998), 8/3 (261-269), 89 reference(s) CODEN: FTCME2 ISSN: 1121-8142
DOCUMENT TYPE: Journal; General Review
COUNTRY: Italy
LANGUAGE: English
SUMMARY LANGUAGE: English

AN 1998:28464352 BIOTECHNO
AB The prognosis of patients with malignant gliomas remains dismal despite the development of a multidisciplinary approach to their treatment. There is a strong need for novel therapeutic approaches that can make a definite impact in the clinical course of these tumours. Although there have been several advances in diagnostic modalities, surgical techniques and cytotoxic therapies, the development of newer therapies has been hampered by the limited understanding of the factors that determine the biological nature of gliomas. However, inroads are now being made into the understanding of the genetic make-up, biological behaviour and therapeutic response of these tumours, which are expected to pave the way for new modes of treatment. In this article, we review the advances made in the identification of potential targets for glioma therapy and the recent clinical trials utilising biological therapies and newer cytotoxic agents.

L8 ANSWER 11 OF 40 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 133:109949 CA
TITLE: Pharmaceutical compositions for treatment of diseased tissues
INVENTOR(S): Lee, Clarence C.; Lee, Feng-Min
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000040269	A2	20000713	WO 2000-US191	20000105 <--
WO 2000040269	A3	20001130		

W: AU, CA, CN, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRIORITY APPLN. INFO.: US 1999-114906P P 19990105
AB A method to treat diseased tissue is provided where a cytotoxic compd. is administered to a patient in need of treatment in combination with an immunostimulant. Diseased cells and/or infectious microbes/viruses are killed by the cytotoxic compd. in the presence of the immunostimulant. The cell components including cellular contents and cell membrane fragments are presented by the immunostimulant to the host animal as antigens to stimulate the immune responses toward other diseased cells of the same type(s), that either remain in the vicinity or reside in distant tissues or organs. The cytotoxic mol. and immunostimulant are preferably applied locally at high concns., either sequentially or, preferably, simultaneously. For example, the compn. can be administered directly to a target cancer. The compn. can be prepd. in various forms, such as a paste, a time release molded solid shape, a soln., a mixt. with emulsifier, etc. Alternatively, the cytotoxic mol. and immunostimulant are applied in sequence.

L8 ANSWER 12 OF 40 CA COPYRIGHT 2003 ACS
ACCESSION NUMBER: 131:346535 CA
TITLE: Use of neomycin for treating angiogenesis-related diseases
INVENTOR(S): Hu, Guo-Fu; Vallee, Bert L.
PATENT ASSIGNEE(S): The Endowment for Research In Human Biology, Inc., USA
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

activity of chemotherapy in metastatic melanoma. Thalidomide (Thalomid) displays antiangiogenic activity and other biological modulatory effects that may provide additive or synergistic antitumor effects when given concurrently with chemotherapy. A phase I/II study of thalidomide and temozolomide in the treatment of metastatic melanoma is in progress. Preliminary studies of this combination therapy have shown significant antitumor activity, including some striking responses in brain metastases.

L8 ANSWER 14 OF 40 CANCERLIT
ACCESSION NUMBER: 1999259140 CANCERLIT
DOCUMENT NUMBER: 99259140 PubMed ID: 10328588
TITLE: New chemotherapy options for the treatment of malignant gliomas.
AUTHOR: Burton E; Prados M
CORPORATE SOURCE: University of California, San Francisco, Department of Neurosurgery, USA.
CONTRACT NUMBER: CA09291 (NCI)
CA13525 (NCI)
SOURCE: CURRENT OPINION IN ONCOLOGY,(1999 May) 11 (3) 157-61. Ref: 24
Journal code: 9007265. ISSN: 1040-8746.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals; AIDS
OTHER SOURCE: MEDLINE 1999259140
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990813
Last Updated on STN: 19990813
AB Chemotherapy remains part of the treatment triad that includes surgery and radiation therapy for the management of malignant gliomas. In recent years there has been an increased understanding of the molecular pathways of malignant transformation. Based on this research, new drugs have been evaluated, with specific cellular targets in mind that can be modified or inhibited. Many of these agents are now being tested in phase I and II clinical trials and have shown some promising results. Clearly, not all patients with malignant gliomas respond equally to chemotherapy. Recent evidence suggests that certain molecular markers may predict chemosensitivity in some tumor types, particularly anaplastic oligodendroglioma. This article reviews recent trends in the use of chemotherapy and clinical trials of new therapies for adults with malignant gliomas.

L8 ANSWER 15 OF 40 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:475560 CAPLUS
DOCUMENT NUMBER: 133:109949
TITLE: Pharmaceutical compositions for treatment of diseased tissues
INVENTOR(S): Lee, Clarence C.; Lee, Feng-Min
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000040269	A2	20000713	WO 2000-US191	20000105 <--
WO 2000040269	A3	20001130		

W: AU, CA, CN, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRIORITY APPLN. INFO.: US 1999-114906P P 19990105
AB A method to treat diseased tissue is provided where a cytotoxic compd. is administered to a patient in need of treatment in combination with an immunostimulant. Diseased cells and/or infectious microbes/viruses are killed by the cytotoxic compd. in the presence of the immunostimulant. The cell components including cellular contents and cell membrane fragments are presented by the immunostimulant to the host animal as antigens to stimulate the immune responses toward other diseased cells of the same type(s), that either remain in the vicinity or reside in distant tissues or organs. The cytotoxic mol. and immunostimulant are preferably applied locally at high concns., either sequentially or, preferably, simultaneously. For example, the compn. can be administered directly to a target cancer. The compn. can be prepd. in various forms, such as a paste, a time release molded solid shape, a soln., a mixt. with emulsifier, etc. Alternatively, the cytotoxic mol. and immunostimulant are applied in sequence.

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9958126	A1	19991118	WO 1999-US10269	19990511 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2331620	AA	19991118	CA 1999-2331620	19990511 <--
AU 9939804	A1	19991129	AU 1999-39804	19990511 <--
EP 1083896	A1	20010321	EP 1999-922915	19990511
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6482802	B1	20021119	US 2000-700436	20001109

PRIORITY APPLN. INFO.: US 1998-84921P P 19980511
WO 1999-US10269 W 19990511
AB The present invention is directed to using neomycin or an analog thereof as a therapeutic agent to treat angiogenesis-related diseases, which are characterized by excessive, undesired or inappropriate angiogenesis or proliferation of endothelial cells. The present invention is also directed to pharmaceutical compns. comprising: (a) neomycin or an analog and, optionally, (b) another anti-angiogenic agent or an anti-neoplastic agent. The present invention is further directed to a method for screening neomycin analogs having anti-angiogenic activity. A preferred embodiment of the invention relates to using neomycin to treat subjects having such diseases. A dose of 20 ng neomycin/embryo or higher completely inhibited angiogenin-induced angiogenesis in the chorioallantoic membrane (CAM) assay. Neomycin inhibits angiogenin-induced angiogenesis mainly through inhibition of nuclear translocation of angiogenin.
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 13 OF 40 CANCERLIT
ACCESSION NUMBER: 2001075767 CANCERLIT
DOCUMENT NUMBER: 21075767 PubMed ID: 11204670
TITLE: New approaches in the treatment of metastatic melanoma: thalidomide and temozolomide.
AUTHOR: Hwu W J
CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, New York, USA.
SOURCE: ONCOLOGY, (2000 Dec) 14 (12 Suppl 13) 25-8. Ref: 16
Journal code: 8712059. ISSN: 0890-9091.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
OTHER SOURCE: MEDLINE 2001192567
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010515
Last Updated on STN: 20010515
AB Although melanoma is a relatively chemoresistant malignancy, systemic chemotherapy remains the primary treatment for metastatic melanoma. The observation of vasculogenic mimicry in aggressive melanoma has prompted investigation into using an antiangiogenic agent to enhance the antitumor

RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRIORITY APPLN. INFO.: US 1999-114906P P 19990105
AB A method to treat diseased tissue is provided where a cytotoxic compd. is administered to a patient in need of treatment in combination with an immunostimulant. Diseased cells and/or infectious microbes/viruses are killed by the cytotoxic compd. in the presence of the immunostimulant. The cell components including cellular contents and cell membrane fragments are presented by the immunostimulant to the host animal as antigens to stimulate the immune responses toward other diseased cells of the same type(s), that either remain in the vicinity or reside in distant tissues or organs. The cytotoxic mol. and immunostimulant are preferably applied locally at high concns., either sequentially or, preferably, simultaneously. For example, the compn. can be administered directly to a target cancer. The compn. can be prepd. in various forms, such as a paste, a time release molded solid shape, a soln., a mixt. with emulsifier, etc. Alternatively, the cytotoxic mol. and immunostimulant are applied in sequence.

L8 ANSWER 16 OF 40 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:736476 CAPLUS
DOCUMENT NUMBER: 131:346535
TITLE: Use of neomycin for treating angiogenesis-related diseases
INVENTOR(S): Hu, Guo-Fu; Vallee, Bert L.
PATENT ASSIGNEE(S): The Endowment for Research In Human Biology, Inc., USA
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9958126	A1	19991118	WO 1999-US10269	19990511 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2331620	AA	19991118	CA 1999-2331620	19990511 <--
AU 9939804	A1	19991129	AU 1999-39804	19990511 <--
EP 1083896	A1	20010321	EP 1999-922915	19990511
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6482802	B1	20021119	US 2000-700436	20001109

PRIORITY APPLN. INFO.: US 1998-84921P P 19980511
WO 1999-US10269 W 19990511
AB The present invention is directed to using neomycin or an analog thereof as a therapeutic agent to treat angiogenesis-related diseases, which are characterized by excessive, undesired or inappropriate angiogenesis or proliferation of endothelial cells. The present invention is also directed to pharmaceutical compns. comprising: (a) neomycin or an analog and, optionally, (b) another anti-angiogenic agent or an anti-neoplastic agent. The present invention is further directed to a method for screening neomycin analogs having anti-angiogenic activity. A preferred embodiment of the invention relates to using neomycin to treat subjects having such diseases. A dose of 20 ng neomycin/embryo or higher completely inhibited angiogenin-induced angiogenesis in the

chorioallantoic membrane (CAM) assay. Neomycin inhibits angiogenin-induced angiogenesis mainly through inhibition of nuclear translocation of angiogenin.
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 17 OF 40 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-15379 DRUGU T S
TITLE: Three-arm Phase II study of temozolomide (TMZ) in metastatic melanoma (MM): preliminary results.
AUTHOR: Arance A; Middleton M; Lorigan P C; Thatcher N
LOCATION: Manchester; Sheffield, U.K.
SOURCE: ; Proc.Am.Soc.Clin.Oncol. (19, 36 Meet., 573a, 2000)
CODEN: ; 7790
AVAIL. OF DOC.: Christie Hospital, Manchester, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 2001-15379 DRUGU T S
AB Preliminary results of a randomized Phase II study of p.o. temozolomide alone or combined with s.c. IFN or procarbadomide in 50 patients with metastatic melanoma are reported. Treatment was active and well-tolerated in all 3 arms, the most common side-effect was myelosuppression. (conference abstract: 36th Annual Meeting of the American Society of Clinical Oncology, New Orleans, Louisiana, USA, 2000).
ABEX 50 Patients (aged 17-78, median 55 yr) with previously untreated metastatic melanoma were randomized to temozolomide 200 mg/sq.m every 8 hr x 5 (18 patients, arm A), temozolomide 200 mg/sq.m days 1-5 and IFN 5 MU thrice weekly for 4 wk (17, arm B) or temozolomide 150 mg/sq.m days 1-5 and thalidomide 100 mg/day for 28 days (15, arm C). Of 43 patients evaluable for response there were 8 PR, 10 disease stabilization and 24 progression. Median overall survival was 6.5 mth and response duration 5.9 mth. Grade 3-4 thrombocytopenia occurred in 36.1% patients with 1 treatment-related death due to intracerebral hemorrhage in a patient with brain metastases. Grade 3-4 leukopenia occurred in 31.9% patients and was more frequent in arms A and B. Grade 1-2 diarrhea was more frequent in arm B. Non-hematological toxicity was mild to moderate and similar in all 3 arms. (E33/JB)

L8 ANSWER 18 OF 40 DRUGU COPYRIGHT 2003 THOMSON DERWENT
ACCESSION NUMBER: 2000-45255 DRUGU T
TITLE: Thalidomide in the treatment of high grade gliomas.
AUTHOR: Cohen M H
CORPORATE SOURCE: FDA
LOCATION: Rockville, Md., USA
SOURCE: J.Clin.Oncol. (18, No. 19, 3453, 2000) 5 Ref.
CODEN: JCONDN ISSN: 0732-183X
AVAIL. OF DOC.: United States Food and Drug Administration, Rockville, MD, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 2000-45255 DRUGU T
AB A letter discusses a recent phase II trial of thalidomide (TH) in the treatment of recurrent high grade gliomas, in which the response was favorable. A recent phase II trial of temozolomide (TE, Temodar, Schering-Plough) in relapsed anaplastic astrocytoma (AA) patients suggested a response superior to TH. The modest TH efficacy in recurrent disease seems too little to warrant a recommendation of addition to first line therapy. Additional studies with drugs additive or synergistic with TH might be useful.

ABEX The recent phase II trial of TH in recurrent high grade gliomas did not differentiate between AA and glioblastoma multiforme, which have very different prognoses. Other prognostic factors (performance status, age, response to primary therapy) favored a positive result for TH. The recent trial of TR in 54 AA patients gave a higher CR rate than TH (5 vs. 0) and a good CR response duration. (YC)

L8 ANSWER 19 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001035295 EMBASE
TITLE: A comparison of treatment results for recurrent malignant gliomas.
AUTHOR: Nieder C.; Grosu A.L.; Molls M.
CORPORATE SOURCE: C. Nieder, Department of Radiation Oncology, Klinikum rechts der Isar, TU Munich, Ismaninger Str. 22, 81675 Munich, Germany
SOURCE: Cancer Treatment Reviews, (2000) 26/6 (397-409).
Refs: 62
ISSN: 0305-7372 CODEN: CTREDJ
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Retreatment of malignant gliomas may be performed with palliative intent after careful consideration of the risks and benefits, and with special regards to iatrogenic neurotoxicity and quality of life (QOL). This review compares studies of several retreatment strategies (published between 1987 and 2000) based on the quality of their evidence. Depending on both established prognostic factors and previous treatment, individually tailored retreatment strategies are possible. In all studies that included a multivariate analysis of prognostic factors, performance status was the most important. So far, predictive factors for response, which might facilitate patient selection, have not been unequivocally defined. In terms of QOL, single-agent chemotherapy (temozolomide, nitrosoureas, platinum and taxane derivatives) may offer a better therapeutic ratio than polychemotherapy. For glioblastoma multiforme, progression-free survival and QOL were more favourable after temozolomide than procarbazine (level I evidence). The survival of patients after various radiotherapy techniques is broadly similar. However, considerable toxicity is associated with radiosurgery or brachytherapy. Fractionated stereotactic radiotherapy plus radio-sensitizing cytostatic agents has shown promising initial results in small groups of selected patients and awaits further evaluation. Level 2 evidence derived from non-randomized studies does not suggest a substantial prolongation of survival by re-resection as compared with chemotherapy or radiotherapy alone. Level I evidence derived from a randomized trial suggests that application of BCNU polymers significantly improves the outcome after re-resection. However, most studies reported median survival in the range of only 25-35 weeks, thereby emphasizing the need for the development and clinical evaluation of new innovative treatment approaches. .COPYRGT. 2000 Harcourt Publishers Ltd.

L8 ANSWER 20 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000429822 EMBASE
TITLE: Novel chemotherapeutic agents for the treatment of brain cancer.
AUTHOR: Newton H.B.
CORPORATE SOURCE: H.B. Newton, Department of Neurology, The Ohio State University Hospitals, 465 Means Hall, 1654 Upham Drive, Columbus, OH 43210, United States. newton.12@osu.edu
SOURCE: Expert Opinion on Investigational Drugs, (2000) 9/12 (2815-2829).
Refs: 97
ISSN: 1354-3784 CODEN: EOIDER
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Brain cancer encompasses both primary and metastatic brain tumours and accounts for over 120,000 new patients each year. Despite aggressive therapy, the majority of patients with brain cancer have poor prognosis and have brief survival intervals. Current chemotherapy drugs, used alone or in combination, have minimal or only modest activity. Novel agents that have recently been applied to brain cancer include temozolomide, irinotecan and paclitaxel. Temozolomide is a DNA alkylating agent, irinotecan inhibits DNA topoisomerase I and paclitaxel binds to microtubules and induces polymerisation. Neoplastic angiogenesis and brain tumour invasion are also targets for therapeutic intervention with new agents such as thalidomide, suramin and marimastat. All of these agents have demonstrated activity against brain cancer in vitro. Several of the drugs, in particular temozolomide, paclitaxel and irinotecan, have entered preliminary clinical trials and have demonstrated some efficacy. However, chemotherapy for primary brain tumours remains rather non-specific and mostly ineffective. The use of chemotherapy may be more effective against selected metastatic brain tumours. Continued basic research is needed to further elucidate the genetic basis of transformation, tumour invasion and angiogenesis. It is hoped that this research will lead to new therapeutic targets for drug design and development. In addition, new strategies must be developed to overcome the problem of chemotherapy resistance.

L8 ANSWER 21 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000426761 EMBASE
TITLE: Chemotherapy in malignant gliomas.
AUTHOR: Burton G.V.
CORPORATE SOURCE: Dr. G.V. Burton, Feist-Weiller Cancer Center, LA State Univ. Health Science Center, 1501 Kings HW, Shreveport, LA 71130-3932, United States
SOURCE: Seminars in Neurosurgery, (2000) 11/3 (373-385).
Refs: 92
ISSN: 1526-8012 CODEN: SNEEAH
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Current chemotherapy approaches to patients with malignant gliomas have little impact on patient outcomes. Surgical and radiotherapy, although providing the majority of benefit, have little potential for significant further improvement of patient survival. Medical therapy, especially with expanding knowledge relative to tumor resistance, oncogenesis pathways, and angiogenesis, has great potential for altering the outcomes of patients with malignant gliomas. New cytotoxic agents such as temozolomide and CPT-11 appear to have significant activity; however, anti-angiogenesis therapy, gene therapies directed at oncogenic pathways, and immuno-toxin constructs may have the greatest potential. Only by participation in clinical trials can these new agents be developed to benefit future patients with malignant gliomas.

L8 ANSWER 22 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000393804 EMBASE
TITLE: Thalidomide in the treatment of high-grade gliomas [4].
AUTHOR: Cohen M.H.
CORPORATE SOURCE: M.H. Cohen, United States Food/Drug Admin., Rockville, MD, United States
SOURCE: Journal of Clinical Oncology, (1 Oct 2000) 18/19 (3453).
Refs: 5
ISSN: 0732-183X CODEN: JCONDN
COUNTRY: United States
DOCUMENT TYPE: Journal; Letter
FILE SEGMENT: 008 Neurology and Neurosurgery
016 Cancer
037 Drug Literature Index
LANGUAGE: English

L8 ANSWER 23 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000356231 EMBASE
TITLE: Chemotherapy: Low-grade gliomas of the hypothalamus and thalamus.
AUTHOR: Packer R.J.
CORPORATE SOURCE: Dr. R.J. Packer, Children's National Medical Center, 111 Michigan Avenue, NW, Washington, DC 20010, United States. rpacker@cnmc.org
SOURCE: Pediatric Neurosurgery, (2000) 32/5 (259-263).
Refs: 20
ISSN: 1016-2291 CODEN: PDNEEV
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
008 Neurology and Neurosurgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Chemotherapy is an increasing component of the management of diencephalic gliomas. It can result in tumor shrinkage and significant disease control in some patients. However, decisions concerning the institution of treatment should be based on the goals of treatment. Factors include: (1) age of the patient; (2) whether the child has neurofibromatosis type 1; (3) tumor size and location; (4) the potential sequelae of radiotherapy, and (5) the acute and long-term toxicity of the chemotherapeutic approach utilized. The erratic natural history of diencephalic tumors confounds evaluation of efficacy of the regimen chosen. Copyright (C) 2000 S. Karger AG, Basel.

L8 ANSWER 24 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000351127 EMBASE
TITLE: Drugs of choice for cancer chemotherapy.
SOURCE: Medical Letter on Drugs and Therapeutics, (18 Sep 2000) 42/1087-1088 (83-92).
ISSN: 0025-732X CODEN: MELEAP
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

L8 ANSWER 25 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000287739 EMBASE
TITLE: [Development of new antineoplastic agents with known and novel mechanisms of action].
ENTWICKLUNG NEUER ANTINEOPLASTISCH WIRKSAMER SUBSTANZEN MIT BEKANNTEN UND NEUEN WIRKUNGSPRINZIPIEN.
AUTHOR: Lipp H.-P.
CORPORATE SOURCE: Dr. H.-P. Lipp, Universitatsapotheke, Rontgenweg 9, 72076

Tubingen, Germany
SOURCE: Krankenhauspharmazie, (2000) 21/8 (396-419).
Refs: 136
ISSN: 0173-7597 CODEN: KRANDZ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English; German
SUMMARY LANGUAGE: English
AB It is a great challenge to find new cytostatics with well-known mechanisms of action which will have (I) a greater therapeutic index, (II) an improved pharmacokinetic behaviour, (III) additional intracellularly located targets or (IV) increased activity against resistant cells. In this regard, examples like Oxaliplatin, TAS-103, CI-941, the Multitargeted Antifolate (MTA), Temozolomide or Eniluracil represent encouraging developments. In the meantime several inhibitors of farnesyl transferases, matrix metalloproteinases, telomerase or different kinases as well as antisense-oligonucleotides or tirapazamine are matter of clinical research. Additionally, substances like SDZ PSC 833 or Benzylguanine may help to overcome multi-resistant conditions.

L8 ANSWER 26 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000218656 EMBASE
TITLE: A review of current and future treatment strategies for malignant astrocytomas in adults.
AUTHOR: Nieder C.; Nestle U.
CORPORATE SOURCE: Dr. U. Nestle, Abteilung fur Strahlentherapie, Radiologische Universitatsklinik, D-66421 Homburg/Saar, Germany. raunes@med-rz.uni-saarland.de
SOURCE: Strahlentherapie und Onkologie, (2000) 176/6 (251-258).
Refs: 81
ISSN: 0179-7158 CODEN: STONE4
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English; German
AB Background: For more than 20 years, after establishing the role of postoperative radiotherapy for malignant astrocytomas, no definitive improvement in survival rates could be observed, despite advances in established treatment modalities such as radiotherapy and chemotherapy. This review discusses available laboratory and clinical data as well as recent advances in our knowledge about prognostic factors (Table 1) and their implications for the design of future clinical trials. Results: Elucidation of the biology of malignant astrocytomas allowed for development of rational new approaches, such as gene therapy and immunotherapy, which could interfere with established treatment regimens or being used independently. Possible strategies include the restoration of defective cancer-inhibitory genes, cell transduction or transfection with antisense DNA corresponding to genes coding for growth factors and their receptors, or with the so-called suicide genes. Several antiangiogenic approaches such as administration of thalidomide, protamine, or monoclonal antibodies against vascular endothelial growth factor have been developed, too. Further treatment possibilities include modulation of drug resistance, e.g. by P-glycoprotein antagonists or O6-alkyl-guanine-DNA-transferase inhibitors, inhibition of matrix metalloproteinases, inhibition of protein kinase C, and administration of agents such as phenylbutyrate or valproic acid that showed promising antiproliferative effects in vitro. Conclusions: Several rational new approaches are now entering clinical trials (Table 2). In the light of limited survival after standard treatment it is recommended that patients should be offered participation in such trials.

L8 ANSWER 27 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000117710 EMBASE
TITLE: Chemotherapy for high-grade gliomas.
AUTHOR: Galanis E.; Buckner J.
CORPORATE SOURCE: E. Galanis, Division of Medical Oncology, Mayo Clinic and Foundation, 200 First Street SW, Rochester, MN 55905, United States
SOURCE: British Journal of Cancer, (2000) 82/8 (1371-1380).
Refs: 117
ISSN: 0007-0920 CODEN: BJCAAI
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

L8 ANSWER 28 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999224768 EMBASE
TITLE: New treatment strategies for malignant gliomas.
AUTHOR: Avgeropoulos N.G.; Batchelor T.T.
CORPORATE SOURCE: Dr. N.G. Avgeropoulos, Massachusetts General Hospital, Brain Tumor Center, 100 Blossom Street, Boston, MA 02114, United States. batchelor@helix.mgh.harvard.edu
SOURCE: Oncologist, (1999) 4/3 (209-224).
Refs: 126
ISSN: 1083-7159 CODEN: OCOLF6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Although survival in patients with malignant gliomas remains limited, there is renewed optimism with the emergence of novel treatment strategies. Cytotoxic agents such as temozolomide and CPT-11 have shown promising clinical activity. Biological treatments for brain tumors, including antisense oligonucleotides, gene therapy, and angiogenesis inhibitors, are also being evaluated in clinical trials. Delivery strategies have been developed to overcome challenges presented by the blood-brain barrier. These noteworthy treatments, alone or in combination, may ultimately prolong survival and enhance quality of life in this group of patients.

L8 ANSWER 29 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999173684 EMBASE
TITLE: New chemotherapy options for the treatment of malignant gliomas.
AUTHOR: Burton E.; Prados M.
CORPORATE SOURCE: Dr. E. Burton, Department of Neurosurgery, M787, San Francisco, CA 94143-0112, United States
SOURCE: Current Opinion in Oncology, (1999) 11/3 (157-161).
Refs: 24
ISSN: 1040-8746 CODEN: CUOOE8
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Chemotherapy remains part of the treatment triad that includes surgery and radiation therapy for the management of malignant gliomas. In recent years there has been an increased understanding of the molecular pathways of malignant transformation. Based on this research, new drugs have been evaluated, with specific cellular targets in mind that can be modified or inhibited. Many of these agents are now being tested in phase I and II clinical trials and have shown some promising results. Clearly, not all patients with malignant gliomas respond equally to chemotherapy. Recent evidence suggests that certain molecular markers may predict chemosensitivity in some tumor types, particularly anaplastic oligodendroglioma. This article reviews recent trends in the use of chemotherapy and clinical trials of new therapies for adults with malignant gliomas.

L8 ANSWER 30 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999069770 EMBASE
TITLE: Innovative therapies for pediatric brain tumors.
AUTHOR: Rubin J.B.; Kieran M.W.
CORPORATE SOURCE: Dr. J.B. Rubin, Dana Farber Cancer Institute, Department of Pediatric Oncology, 44 Binney Street, Boston, MA 02115, United States
SOURCE: Current Opinion in Pediatrics, (1999) 11/1 (39-46).
Refs: 143
ISSN: 1040-8703 CODEN: COPEE
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
014 Radiology
016 Cancer
022 Human Genetics
026 Immunology, Serology and Transplantation
027 Biophysics, Bioengineering and Medical Instrumentation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Success in the treatment of pediatric brain tumors has lagged behind that of other pediatric cancers. This paper highlights many of the advances that have taken place over the past few years in the surgical, radiotherapeutic, and chemotherapeutic approaches to central nervous system lesions that we hope will lead to a dramatic improvement in outcome. Innovations in neurosurgical and radiotherapeutic techniques have resulted in decreasing toxicity although substantial improvement in cure rates has not been observed. Many new techniques such as gene therapy, angiogenesis inhibitors, immunotherapy, and others that have not been part of the classic approach to these lesions are now in clinical trials in the hope that they will impact on the survival of these patients. The scientific basis for these new treatment modalities and preliminary clinical results are discussed.

L8 ANSWER 31 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998341815 EMBASE
TITLE: New frontiers in therapy of malignant gliomas.
AUTHOR: Puduvalli V.K.; Yung W.K.A.
CORPORATE SOURCE: W.K.A. Yung, Department of Neuro-oncology, The University of Texas, M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, United States
SOURCE: FORUM - Trends in Experimental and Clinical Medicine, (1998) 8/3 (261-269).
Refs: 89
ISSN: 1121-8142 CODEN: FTCME2
COUNTRY: Italy
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The prognosis of patients with malignant gliomas remains dismal despite the development of a multidisciplinary approach to their treatment. There is a strong need for novel therapeutic approaches that can make a definite impact in the clinical course of these tumours. Although there have been several advances in diagnostic modalities, surgical techniques and cytotoxic therapies, the development of newer therapies has been hampered by the limited understanding of the factors that determine the biological nature of gliomas. However, inroads are now being made into the understanding of the genetic make-up, biological behaviour and therapeutic response of these tumours, which are expected to pave the way for new modes of treatment. In this article, we review the advances made in the identification of potential targets for glioma therapy and the recent clinical trials utilising biological therapies and newer cytotoxic agents.

L8 ANSWER 32 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97049528 EMBASE
DOCUMENT NUMBER: 1997049528
TITLE: Recognition and management of gliomas.
AUTHOR: Kaba S.E.; Kyritsis A.P.
CORPORATE SOURCE: Dr. S.E. Kaba, Department of Neurology, UAMS, 4301 W. Markham Street, Little Rock, AR 72205, United States
SOURCE: Drugs, (1997) 53/2 (235-244).
Refs: 56
ISSN: 0012-6667 CODEN: DRUGAY
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Gliomas are the most frequent primary brain tumours. They include astrocytic gliomas, oligodendrocytic gliomas, ependymomas and gliomas with mixed cell populations. Each glioma type consists of both low-grade and malignant atypical varieties. The low-grade rumours occur predominantly in children and young adults, and the malignant forms in older people. The presenting symptoms are epileptic seizures, headache and mental confusion. Focal neurological symptoms and findings, such as hemiparesis, are mostly associated with the malignant forms. Magnetic resonance imaging (MRI) scan of the brain with and without gadolinium contrast demonstrates the tumour. However, stereotactic biopsy or surgical resection is necessary to obtain the correct pathological diagnosis, except for diffuse pontine astrocytomas, which have an unmistakeable imaging appearance and for which biopsy has substantial risks. Treatment depends on the pathological diagnosis. Complete surgical resection may be curative for low-grade tumours. Postoperative radiotherapy is recommended for partially resected rumours. Most malignant gliomas require aggressive combination therapy with radiotherapy and chemotherapy after maximal surgery. The standard initial regimens are nitrosourea-based chemotherapies, such as carmustine alone, a combination of procarbazine, lomustine and vincristine, or a combination of thioguanine, procarbazine, lomustine and hydroxycarbamide (hydroxyurea). Unfortunately, the prognosis of malignant gliomas is

generally poor despite aggressive treatment, because of their infiltrative nature and high relapse rate.

L8 ANSWER 33 OF 40 MEDLINE
ACCESSION NUMBER: 2001192567 MEDLINE
DOCUMENT NUMBER: 21075767 PubMed ID: 11204670
TITLE: New approaches in the treatment of metastatic melanoma: thalidomide and temozolomide.
AUTHOR: Hwu W J
CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, New York, USA.
SOURCE: ONCOLOGY, (2000 Dec) 14 (12 Suppl 13) 25-8. Ref: 16
Journal code: 8712059. ISSN: 0890-9091.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010410
Last Updated on STN: 20010410
Entered Medline: 20010405

AB Although melanoma is a relatively chemoresistant malignancy, systemic chemotherapy remains the primary treatment for metastatic melanoma. The observation of vasculogenic mimicry in aggressive melanoma has prompted investigation into using an antiangiogenic agent to enhance the antitumor activity of chemotherapy in metastatic melanoma. Thalidomide (Thalomid) exhibits antiangiogenic activity and other biological modulatory effects that may provide additive or synergistic antitumor effects when given concurrently with chemotherapy. A phase I/II study of thalidomide and temozolomide in the treatment of metastatic melanoma is in progress. Preliminary results of this combination therapy have shown significant antitumor activity, including some striking responses in brain metastases.

L8 ANSWER 34 OF 40 MEDLINE
ACCESSION NUMBER: 1999259140 MEDLINE
DOCUMENT NUMBER: 99259140 PubMed ID: 10328588
TITLE: New chemotherapy options for the treatment of malignant gliomas.
AUTHOR: Burton E; Prados M
CORPORATE SOURCE: University of California, San Francisco, Department of Neurosurgery, USA.
CONTRACT NUMBER: CA09291 (NCI)
CA13525 (NCI)
SOURCE: CURRENT OPINION IN ONCOLOGY, (1999 May) 11 (3) 157-61. Ref: 24
Journal code: 9007265. ISSN: 1040-8746.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990714
Last Updated on STN: 19990714
Entered Medline: 19990628

AB Chemotherapy remains part of the treatment triad that includes surgery and radiation therapy for the management of malignant gliomas. In recent years there has been an increased understanding of the molecular pathways of malignant transformation. Based on this research, new drugs have been evaluated, with specific cellular targets in mind that can be modified or inhibited. Many of these agents are now being tested in phase I and II clinical trials and have shown some promising results. Clearly, not all patients with malignant gliomas respond equally to chemotherapy. Recent evidence suggests that certain molecular markers may predict chemosensitivity in some tumor types, particularly anaplastic oligodendroglioma. This article reviews recent trends in the use of chemotherapy and clinical trials of new therapies for adults with malignant gliomas.

L8 ANSWER 35 OF 40 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:30005 TOXCENTER
DOCUMENT NUMBER: 21075767 PubMed ID: 11204670
TITLE: New approaches in the treatment of metastatic melanoma: thalidomide and temozolomide
AUTHOR(S): Hwu W J
CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, New York, USA
SOURCE: ONCOLOGY, 2000 Dec) 14 (12 Suppl 13) 25-8. Ref: 16.
Journal Code: 8712059. ISSN: 0890-9091.
COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
FILE SEGMENT: MEDLINE
OTHER SOURCE: MEDLINE 2001192567
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20011116

AB Although melanoma is a relatively chemoresistant malignancy, systemic chemotherapy remains the primary treatment for metastatic melanoma. The observation of vasculogenic mimicry in aggressive melanoma has prompted investigation into using an antiangiogenic agent to enhance the antitumor activity of chemotherapy in metastatic melanoma. Thalidomide (Thalomid) exhibits antiangiogenic activity and other biological modulatory effects that may provide additive or synergistic antitumor effects when given concurrently with chemotherapy. A phase I/II study of thalidomide and temozolomide in the treatment of metastatic melanoma is in progress. Preliminary results of this combination therapy have shown significant antitumor activity, including some striking responses in brain metastases.

L8 ANSWER 36 OF 40 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:168159 TOXCENTER
COPYRIGHT: Copyright 2003 ACS
DOCUMENT NUMBER: CA13308109949G
TITLE: Pharmaceutical compositions for treatment of diseased tissues
AUTHOR(S): Lee, Clarence C.; Lee, Feng-Min
PATENT INFORMATION: WO 2000040269 A2 13 Jul 2000
SOURCE: 2000) PCT Int. Appl., 26 pp.
CODEN: PIXXD2.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Patent
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 2000:475560
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20020326

AB A method to treat diseased tissue is provided where a cytotoxic compd. is administered to a patient in need of treatment in combination with an immunostimulant. Diseased cells and/or infectious microbes/viruses are killed by the cytotoxic compd. in the presence of the immunostimulant. The cell components including cellular contents and cell membrane fragments are presented by the immunostimulant to the host animal as antigens to stimulate the immune responses toward other diseased cells of the same type(s), that either remain in the vicinity or reside in distant tissues or organs. The cytotoxic mol. and immunostimulant are preferably applied locally at high concns., either sequentially or, preferably, simultaneously. For example, the compn. can be administered directly to a targst cancer. The compn. can be prepd. in various forms, such as a paste, a time release molded solid shape, a soln., a mixt. with emulsifier, etc. Alternatively, the cytotoxic mol. and immunostimulant are applied in sequence.

L8 ANSWER 37 OF 40 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:208077 TOXCENTER
COPYRIGHT: Copyright 2003 ACS
DOCUMENT NUMBER: CA13126346535K
TITLE: Use of neomycin for treating angiogenesis-related diseases
AUTHOR(S): Hu, Guo-Fu; Valles, Bert L.
CORPORATE SOURCE: ASSIGNEE: The Endowment for Research In Human Biology, Inc.
PATENT INFORMATION: WO 9958126 A1 18 Nov 1999
SOURCE: 1999) PCT Int. Appl., 74 pp.
CODEN: PIXXD2.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Patent
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 1999:736476
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20030225

AB The present invention is directed to using neomycin or an analog thereof as a therapeutic agent to treat angiogenesis-related diseases, which are characterized by excessive, undesired or inappropriate angiogenesis or proliferation of endothelial cells. The present invention is also directed to pharmaceutical compns. comprising: (a) neomycin or an analog and, optionally, (b) another anti-angiogenic agent or an anti-neoplastic agent. The present invention is further directed to a method for screening neomycin analogs having anti-angiogenic activity. A preferred embodiment of the invention relates to using neomycin to treat subjects having such diseases. A dose of 20 ng neomycin/embryo or higher completely inhibited angiogenin-induced angiogenesis in the chorioallantoic membrane (CAM) assay. Neomycin inhibits angiogenin-induced angiogenesis mainly through inhibition of nuclear translocation of angiogenin.

L8 ANSWER 38 OF 40 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:40314 TOXCENTER
DOCUMENT NUMBER: 99259140 PubMed ID: 10328588
TITLE: New chemotherapy options for the treatment of malignant gliomas
AUTHOR(S): Burton E; Prados M
CORPORATE SOURCE: University of California, San Francisco, Department of Neurosurgery, USA
CONTRACT NUMBER: CA09291 (NCI)
CA13525 (NCI)
SOURCE: CURRENT OPINION IN ONCOLOGY, 1999 May) 11 (3) 157-61. Ref: 24.
Journal Code: 9007265. ISSN: 1040-8746.
COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
FILE SEGMENT: MEDLINE
OTHER SOURCE: MEDLINE 1999259140
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20011116

AB Chemotherapy remains part of the treatment triad that includes surgery and radiation therapy for the management of malignant gliomas. In recent years there has been an increased understanding of the molecular pathways of malignant transformation. Based on this research, new drugs have been evaluated, with specific cellular targets in mind that can be modified or inhibited. Many of these agents are now being tested in phase I and II clinical trials and have shown some promising results. Clearly, not all patients with malignant gliomas respond equally to chemotherapy. Recent evidence suggests that certain molecular markers may predict chemosensitivity in some tumor types, particularly anaplastic oligodendroglioma. This article reviews recent trends in the use of chemotherapy and clinical trials of new therapies for adults with malignant gliomas.

L8 ANSWER 39 OF 40 USPATFULL
ACCESSION NUMBER: 2002:303979 USPATFULL
TITLE: Use of neomycin for treating angiogenesis-related diseases
INVENTOR(S): Hu, Guo-fu, Brookline, MA, United States
Valles, Bert L., Boston, MA, United States
PATENT ASSIGNEE(S): Endowment for Research in Human Biology, Inc., Boston, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6482802	B1	20021119	
	WO 9958126		19991118	<--
APPLICATION INFO.:	US 2000-700436		20001109	(9)
	WO 1999-US10269		19990511	
			20001109	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-84921P	19980511 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Raymond, Richard L.
LEGAL REPRESENTATIVE: Pennie & Edmonds LLP
NUMBER OF CLAIMS: 63
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 4 Drawing Page(s)
LINE COUNT: 2312
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to using neomycin or an analogue thereof as an therapeutic agent to treat angiogenesis-related diseases, which are characterized by excessive, undesired or inappropriate angiogenesis or proliferation of endothelial cells. The present invention is also directed to pharmaceutical compositions comprising (a) neomycin or an analogue and, optionally, (b) another anti-angiogenic agent or an anti-neoplastic agent. The present invention is further directed to a method for screening neomycin analogues having anti-angiogenic activity. A preferred embodiment of the invention relates to using neomycin to treat subjects having such diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 40 OF 40 USPATFULL
ACCESSION NUMBER: 2000:37315 USPATFULL
TITLE: Injection-molding apparatus and method of injection-molding
INVENTOR(S): Abe, Masaharu, Otake, Japan
Takaragi, Shigeru, Otake, Japan
Yamamoto, Hiroshi, Otake, Japan

Nakamura, Kyoichi, Otake, Japan
Sasaki, Osamu, Otake, Japan
PATENT ASSIGNEE(S): Toda Kogyo Corporation, Japan (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6042757		20000328	<--
APPLICATION INFO.:	US 1998-84921		19980528	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1997-157552	19970529

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Heitbrink, Jill L.
LEGAL REPRESENTATIVE: Nixon & Vanderhye
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 728
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB An injection-molding device including an injection machine, a mold unit connected to the injection machine having separable molds defining a cavity for forming a molded product, and chucks next to the mold unit for removing a molded product from the mold. The molded product is initially coolied in the mold cavity then again cooled after removal from the mold unit. Plural chucks are advanced into and retreated from a region defined by the open molds, the chucks being a pair of blocks grasping the surface of the molded product, each block having a circulating path through which a heating medium is passed to cool the grasping surface. The injection-molding apparatus produces articles having high dimensional accuracy, for example, electronic parts such as a magnet roll or the like.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> FIL HOME

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	180.61	326.72

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-2.54	-2.54

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=> dis l8 all 1-40
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L8 ANSWER 1 OF 40 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1999:363934 BIOSIS
DN PREV199900363934
TI New chemotherapy options for the treatment of malignant gliomas.
AU Burton, Eric (1); Prados, Michael
CS (1) Department of Neurosurgery M787, San Francisco, CA, 94143-0112 USA
SO Current Opinion in Oncology, May, 1999) Vol. 11, No. 3, pp. 157-161.
ISSN: 1040-8746.
DT Article
LA English
CC Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
Cardiovascular System - Physiology and Biochemistry *14504
Nervous System - Pathology *20506
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Cardiovascular System *22010
Pharmacology - Neuropharmacology *22024
Biochemical Studies - General *10060
Pathology, General and Miscellaneous - Therapy *12512
BC Hominidae 86215
IT Major Concepts
Oncology (Human Medicine, Medical Sciences); Pharmacology
IT Diseases
malignant glioma: neoplastic disease, nervous system disease, new chemotherapy options
IT Chemicals & Biochemicals
irinotecan: antineoplastic - drug; lomustine: antineoplastic - drug, combination therapy; procarbazine: antineoplastic - drug, combination therapy; temozolomide: antineoplastic - drug; thalidomide: angiogenesis inhibitor, antineoplastic - drug; vincristine: antineoplastic - drug, combination therapy
IT Alternate Indexing
Glioma (MeSH)
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae): patient
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates
RN 85622-93-1 (TEMOZOLOMIDE)
97682-44-5 (IRINOTECAN)
50-35-1 (THALIDOMIDE)
671-16-9 (PROCARBAZINE)
13010-47-4 (LOMUSTINE)
57-22-7 (VINCRISTINE)

L8 ANSWER 2 OF 40 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
AN 2000:32094859 BIOTECHNO
TI A comparison of treatment results for recurrent malignant gliomas
AU Nieder C.; Grosu A.L.; Molls M.
CS C. Nieder, Department of Radiation Oncology, Klinikum rechts der Isar, TU Munich, Ismaninger Str. 22, 81675 Munich, Germany.
SO Cancer Treatment Reviews, 2000), 26/6 (397-409), 62 reference(s)
CODEN: CTREDJ ISSN: 0305-7372
DT Journal; General Review
CY United Kingdom
LA English
SL English
AB Retreatment of malignant gliomas may be performed with palliative intent after careful consideration of the risks and benefits, and with special regards to iatrogenic neurotoxicity and quality of life (QOL). This review compares studies of several retreatment strategies (published between 1987 and 2000) based on the quality of their evidence. Depending on both established prognostic factors and previous treatment, individually tailored retreatment strategies are possible. In all studies that included a multivariate analysis of prognostic factors, performance status was the most important. So far, predictive factors for response, which might facilitate patient selection, have not been unequivocally defined. In terms of QOL, single-agent chemotherapy (temozolomide, nitrosoureas, platinum and taxane derivatives) may offer a better therapeutic ratio than polychemotherapy. For glioblastoma multiforme, progression-free survival and QOL were more favourable after temozolomide than procarbazine (level I evidence). The survival of patients after various radiotherapy techniques is broadly similar. However, considerable toxicity is associated with radiosurgery or brachytherapy. Fractionated stereotactic radiotherapy plus radio-sensitizing cytostatic agents has shown promising initial results in small groups of selected patients and awaits further evaluation. Level 2 evidence derived from non-randomized studies does not suggest a substantial prolongation of survival by re-resection as compared with chemotherapy or radiotherapy alone. Level I evidence derived from a randomized trial suggests that application of BCNU polymers significantly improves the outcome after re-resection. However, most studies reported median survival in the range of only 25-35 weeks, thereby emphasizing the need for the development and clinical evaluation of new innovative treatment approaches. .COPYRGT. 2000 Harcourt Publishers Ltd.
CT *glioblastoma; cancer grading; recurrent cancer; cancer palliative therapy; neurotoxicity; quality of life; prognosis; evidence based medicine; patient selection; cancer chemotherapy; monotherapy; cancer survival; brachytherapy; radiosurgery; stereotaxic surgery; gene therapy; constipation; somnolence; comparative study; human; clinical trial; randomized controlled trial; controlled study; review; temozolomide; nitrosourea derivative; platinum derivative; taxane derivative; procarbazine; radiosensitizing agent; cytostatic agent; carmustine; carboplatin; etoposide; ifosfamide; lomustine; benznidazole; alpha interferon; tamoxifen; anthracycline antibiotic agent; taxol; irinotecan; retinoic acid; cisplatin; thalidomide
RN (temozolomide) 85622-93-1; (procarbazine) 366-70-1, 671-16-9; (carmustine) 154-93-8; (carboplatin) 41575-94-4; (etoposide) 33419-42-0; (ifosfamide) 3778-73-2; (lomustine) 13010-47-4; (benznidazole) 22994-85-0; (tamoxifen) 10540-29-1; (taxol) 33069-62-4; (irinotecan) 100286-90-6; (retinoic acid)_302-79-4; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (thalidomide)50-35-1

L8 ANSWER 3 OF 40 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
AN 2000:30981156 BIOTECHNO
TI Chemotherapy in malignant gliomas
AU Burton G.V.
CS Dr. G.V. Burton, Feist-Weiller Cancer Center, LA State Univ. Health Science Center, 1501 Kings HW, Shreveport, LA 71130-3932, United States.
SO Seminars in Neurosurgery, 2000), 11/3 (373-385), 92 reference(s)
CODEN: SNEEAH ISSN: 1526-8012
DT Journal; General Review
CY United States
LA English
SL English
AB Current chemotherapy approaches to patients with malignant gliomas have little impact on patient outcomes. Surgical and radiotherapy, although providing the majority of benefit, have little potential for significant further improvement of patient survival. Medical therapy, especially with expanding knowledge relative to tumor resistance, oncogenesis pathways, and angiogenesis, has great potential for altering the outcomes of patients with malignant gliomas. New cytotoxic agents such as temozolomide and CPT-11 appear to have significant activity; however, anti-angiogenesis therapy, gene therapies directed at oncogenic pathways, and immuno-toxin constructs may have the greatest potential. Only by participation in clinical trials can these new agents be developed to benefit future patients with malignant gliomas.
CT *glioblastoma; *antineoplastic agent; *angiogenesis inhibitor; *thalidomide; *nalpha [2 [arginylprolyl(4 hydroxyprolyl)glycyl[3 (2 thienyl)alanyl]serylprolylamino) 3 (4 methoxyphenyl)propyl]arginine; *BCG vaccine; *picibanil; *levamisole; *interferon; *immunotoxin; *polymer; treatment outcome; cancer survival; cancer resistance; carcinogenesis; angiogenesis; prognosis; drug effect; gene therapy; drug efficacy; drug cytotoxicity; drug activity; cancer immunotherapy; adoptive immunotherapy; multimodality cancer therapy; cancer adjuvant therapy; human; review; lomustine; carmustine; semustine; teniposide; meprednisone; procarbazine; mitolactol; dacarbazine; streptozocin; misonidazole; hydroxyurea; fluorouracil; diaziquone; 1 (2 chloroethyl) 3 (2,6 dioxo 3 piperidyl) 1 nitrosourea; mitomycin C; mercaptopurine; broxuridine; temozolomide; irinotecan; unindexed drug
RN (thalidomide) 50-35-1; (nalpha [2 [arginylprolyl(4 hydroxyprolyl)glycyl[3 (2 thienyl)alanyl]serylprolylamino) 3 (4 methoxyphenyl)propyl]arginine) 159768-75-9; (picibanil) 39325-01-4; (levamisole) 14769-73-4, 16595-80-5; (lomustine) 13010-47-4; (carmustine) 154-93-8; (semustine) 13909-09-6; (teniposide) 29767-20-2; (meprednisone) 1247-42-3; (procarbazine) 366-70-1, 671-16-9; (mitolactol) 10318-26-0; (dacarbazine) 4342-03-4; (streptozocin) 18883-66-4; (misonidazole) 13551-87-6; (hydroxyurea) 127-07-1; (fluorouracil) 51-21-8; (diaziquone) 57998-68-2; (1 (2 chloroethyl) 3 (2,6 dioxo 3 piperidyl) 1 nitrosourea) 13909-02-9; (mitomycin C) 50-07-7, 74349-48-7; (mercaptopurine) 31441-78-8, 50-44-2, 6112-76-1; (broxuridine) 59-14-3; (temozolomide) 85622-93-1; (irinotecan) 100286-90-6

L8 ANSWER 4 OF 40 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
AN 2000:30744566 BIOTECHNO
TI Drugs of choice for cancer chemotherapy
SO Medical Letter on Drugs and Therapeutics,(18 SEP 2000), 42/1087-1088 (83-92)
CODEN: MELEAP ISSN: 0025-732X
DT Journal; General Review
CY United States
LA English
CT *cancer chemotherapy; *cancer; *antineoplastic agent; drug choice; drug indication; United States; Canada; food and drug administration; cancer surgery; cancer radiotherapy; acute toxicity; chronic toxicity; cancer combination chemotherapy; bone marrow depression; mouth ulcer; digestive system ulcer; kidney injury; hypophosphatemia; human; review; cisplatin; etoposide; mithramycin; UFT; 9 cis retinoic acid; altretamine; anastrozole; asparaginase; azacitidine; 4 [1 (5,6,7,8 tetrahydro 3,5,5,8,8 pentamethyl 2 naphthyl]ethenyl]benzoic acid; BCG vaccine; denileukin diftitox; epirubicin; gemtuzumab; alpha2b interferon; temozolomide; thalidomide; cytarabine; dacarbazine; dactinomycin; daunorubicin; diethylstilbestrol; estramustine phosphate sodium; floxuridine; fludarabine phosphate; fluorouracil; fluoxymesterone; flutamide; unindexed drug; unclassified drug; theracys; bicalutamide; bleomycin sulfate; busulfan; capecitabine; carboplatin; carmustine; chlorambucil; 2 chlorodeoxyadenosine; cyclophosphamide; fosfestrol; taxotere; doxorubicin; ellence; exemestane; gallium nitrate; gemcitabine; mylotarg; goserelin; hydroxyurea; idarubicin; ifosfamide; recombinant alpha2a interferon; recombinant alpha2b interferon; alphan3 interferon; recombinant interleukin 2; irinotecan; isotretinoin; letrozole; folinate calcium; leuprorelin; lomustine; chlormethine; megestrol acetate; melphalan; mercaptopurine; mesna; methotrexate; mitomycin C; mitotane; mitoxantrone; nilutamide; octreotide; oxaliplatin; taxol; asparaginase macrogol; pentostatin; mithricin; procarbazine; rituximab; streptozocin; tamoxifen citrate; temodar; teniposide; thiotepa; topotecan; toremifene; trastuzumab; retinoic acid; valrubicin; vinblastine sulfate; vincristine sulfate; navelbine; tioguanine; aminoglutethimide; chlorozotocin; medroxyprogesterone acetate; tarabine; etretinate; thalidomid
RN (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (etoposide) 33419-42-0; (mithramycin) 18378-89-7; (UFT) 74578-38-4; (altretamine) 15468-34-5, 2975-00-0, 645-05-6; (anastrozole) 120511-73-1; (asparaginase) 9015-68-3; (azacitidine) 320-67-2, 52934-49-3; (4 [1 (5,6,7,8 tetrahydro 3,5,5,8,8 pentamethyl 2 naphthyl)ethenyl]benzoic acid) 153559-49-0; (epirubicin) 56390-09-1, 56420-45-2; (alpha2b interferon) 99210-65-8; (temozolomide) 85622-93-1; (thalidomide) 50-35-1; (cytarabine) 147-94-4, 69-74-9; (dacarbazine) 4342-03-4; (dactinomycin) 1402-38-6, 1402-58-0, 50-76-0; (daunorubicin) 12707-28-7, 20830-81-3, 23541-50-6; (diethylstilbestrol) 30498-65-2, 56-53-1; (estramustine phosphate sodium)

52205-73-9; (floxuridine) 50-91-9; (fludarabine phosphate) 75607-67-9; (fluorouracil) 51-21-8; (fluoxymesterone) 76-43-7; (flutamide) 13311-84-7; (bicalutamide) 90357-06-5; (bleomycin sulfate) 9041-93-4; (busulfan) 55-98-1; (capecitabine) 154361-50-9; (carboplatin) 41575-94-4; (carmustine) 154-93-8; (chlorambucil) 305-03-3; (2 chlorodeoxyadenosine) 4291-63-8; (cyclophosphamide) 50-18-0; (fosfestrol) 4719-75-9, 522-40-7; (taxotere) 114977-28-5; (doxorubicin) 23214-92-8, 25316-40-9; (exemestane) 107868-30-4; (gallium nitrate) 13494-90-1; (gemcitabine) 103882-84-4; (goserelin) 65807-02-5; (hydroxyurea) 127-07-1; (idarubicin) 57852-57-0, 58957-92-9; (ifosfamide) 3778-73-2; (recombinant alpha2b interferon) 98530-12-2; (recombinant interleukin 2) 110942-02-4; (irinotecan) 100286-90-6; (isotretinoin) 4759-48-2; (letrozole) 112809-51-5; (folinate calcium) 1492-18-8, 51057-63-7; (leuprorelin) 53714-56-0, 74381-53-6; (lomustine) 13010-47-4; (chlormethine) 51-75-2, 55-86-7, 82905-71-3; (megestrol acetate) 595-33-5; (melphalan) 148-82-3; (mercaptopurine) 31441-78-8, 50-44-2, 6112-76-1; (mesna) 19767-45-4, 3375-50-6; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5

CN Drug Trade Name: panretin; hexalen; arimidex; elspar; mylosar; targretin; theracys; casodex; blenoxane; myleran; xeloda; paraplatin; bicnu; gliadel; leukeran; platinol; leustatin; cytoxan; neosar; cytosar u; dtic dome; cosmegen; cerubidine; daunoxome; ontak; stilphostrol; taxotere; adriamycin; doxil; ellence; emcyt; vepesid; aromasin; fudr; fludara; adrucil; halotestin; eulexin; ganite; gemzar; mylotarg; zoladex; hydrea; idamycin; ifex; roferon a; intron A; alferon n; proleukin; camptosar; accutane; femara; wellcovorin; lupron; lupron depot; ceenu; mustargen; megace; alkeran; purinethol; mesnex; folex; mutamycin; lysodren; novantrone; nilandron; sandostatin; eloxatine; taxol; oncaspar; nipent; mithricin; matulane; rituxan; zanosar; nolvadex; temodar; vumon; thalomid; thioplex; hycamtin; fareston; herceptin; vesanoid; valstar; velban; oncovin; navelbine; kidrolase; pharmorubicin; euflex; uromitexan; natulan; tamofen; lanvis; velbe; cytadren; dcnu; depo provera; provera; rubex; tarabine; tegison; UFT; vincasar; thalidomid

CO Drug Manufacturer: Ligand Pharmaceuticals; United States Bioscience; Zeneca; Merck; Pharmacia Upjohn; Connaught; Bristol; Glaxo Wellcome; Hoffmann La Roche; Rhone Poulenc Rorer; Ortho; Bayer; Bedford; Gilead; Alza; Berlex; Schering; Solopak; Lilly; Wyeth Ayerst; Interferon Laboratories; Chiron; Novartis; TAP; Immunex; Hoechst Marion Roussel; Sanofi Synthelabo; Supergen; Pfizer; Idec; Schering Plough; Celgene; SmithKline Beecham; Genentech; Medeva

L8 ANSWER 5 OF 40 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
AN 2000:30627466 BIOTECHNO
TI Development of new antineoplastic agents with known and novel mechanisms of action
ENTWICKLUNG NEUER ANTINEOPLASTISCH WIRKSAMER SUBSTANZEN MIT BEKANNTEN UND NEUEN WIRKUNGSPRINZIPIEN
AU Lipp H.-P.
CS Dr. H.-P. Lipp, Universitatsapotheke, Rontgenweg 9, 72076 Tubingen, Germany.
SO Krankenhauspharmazie, 2000), 21/8 (396-419), 136 reference(s)
CODEN: KRANDZ ISSN: 0173-7597
DT Journal; Article
CY Germany, Federal Republic of
LA English; German
SL English
AB It is a great challenge to find new cytostatics with well-known mechanisms of action which will have (I) a greater therapeutic index, (II) an improved pharmacokinetic behaviour, (III) additional intracellularly located targets or (IV) increased activity against resistant cells. In this regard, examples like Oxaliplatin, TAS-103, CI-941, the Multitargeted Antifolate (MTA), Temozolomide or Eniluracil represent encouraging developments. In the meantime several inhibitors of farnesyl transferases, matrix metalloproteinases, telomerase or different kinases as well as antisense-oligonucleotides or tirapazamine are matter of clinical research. Additionally, substances like SDZ PSC 833 or Benzylguanine may help to overcome multi-resistant conditions.

CT *antineoplastic agent; *alkylating agent; *DNA topoisomerase inhibitor; *anthracycline antibiotic agent; *folic acid antagonist; *antisense oligonucleotide; *cancer chemotherapy; antineoplastic antibiotic; temozolomide; penclomedine; camptothecin derivative; 9 aminocamptothecin; rebeccamycin; losoxantrone; methotrexate derivative; tomudex; lometrexol; fluorouracil derivative; capecitabine; 5 ethynyluracil; edelfosine; perifosine; miltefosine; Vinca alkaloid; vinflunine; angiogenesis inhibitor; fumagillol chloroacetylcarbamate; marimastat; thalidomide; angiostatin; unindexed drug; cancer research; drug research; antineoplastic activity; drug mechanism; drug structure; drug metabolism; cancer; drug induced disease; neurotoxicity; bone marrow toxicity; melanoma; human; clinical trial; phase 1 clinical trial; article

RN (temozolomide) 85622-93-1; (penclomedine) 108030-77-9; (rebeccamycin) 93908-02-2; (losoxantrone) 88303-60-0; (tomudex) 112887-68-0; (lometrexol) 106400-18-4, 106400-81-1, 120408-07-3, 95693-76-8; (capecitabine) 154361-50-9; (5 ethynyluracil) 59989-18-3; (edelfosine) 65492-82-2; (perifosine) 157716-52-4; (miltefosine) 58066-85-6; (vinflunine) 162652-95-1; (fumagillol chloroacetylcarbamate) 129298-91-5; (marimastat) 154039-60-8; (thalidomide)50-35-1; (angiostatin) 172642-30-7, 86090-08-6

CN Drug Trade Name: temodal; ci 941; zn d1694; ly 264618; xeloda; miltex

L8 ANSWER 6 OF 40 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
AN 2000:30407535 BIOTECHNO
TI A review of current and future treatment strategies for malignant astrocytomas in adults
AU Nieder C.; Nestle U.
CS Dr. U. Nestle, Abteilung fur Strahlentherapie, Radiologische Universitatsklinik, D-66421 Homburg/Saar, Germany.
E-mail: raunes@med-rz.uni-saarland.de
SO Strahlentherapie und Onkologie, 2000), 176/6 (251-258), 81 reference(s)
CODEN: STONR4 ISSN: 0179-7158
DT Journal; General Review
CY Germany, Federal Republic of
LA English
SL English; German
AB Background: For more than 20 years, after establishing the role of postoperative radiotherapy for malignant astrocytomas, no definitive improvement in survival rates could be observed, despite advances in established treatment modalities such as radiotherapy and chemotherapy. This review discusses available laboratory and clinical data as well as recent advances in our knowledge about prognostic factors (Table 1) and their implications for the design of future clinical trials. Results: Elucidation of the biology of malignant astrocytomas allowed for development of rational new approaches, such as gene therapy and immunotherapy, which could interfere with established treatment regimens or being used independently. Possible strategies include the restoration of defective cancer-inhibitory genes, cell transduction or transfection with antisense DNA corresponding to genes coding for growth factors and their receptors, or with the so-called suicide genes. Several antiangiogenic approaches such as administration of thalidomide, protamine, or monoclonal antibodies against vascular endothelial growth factor have been developed, too. Further treatment possibilities include modulation of drug resistance, e.g. by P-glycoprotein antagonists or O6-alkyl-guanine-DNA-transferase inhibitors, inhibition of matrix metalloproteinases, inhibition of protein kinase C, and administration of agents such as phenylbutyrate or valproic acid that showed promising antiproliferative effects in vitro. Conclusions: Several rational new approaches are now entering clinical trials (Table 2). In the light of limited survival after standard treatment it is recommended that patients should be offered participation in such trials.

CT *thalidomide; *protamine; *astrocytoma; glycoprotein P; vasculotropin; matrix metalloproteinase inhibitor; protein kinase inhibitor; carmustine; procarbazine; hydroxyurea; teniposide; taxol; topotecan; irinotecan; temozolomide; 2 chlorodeoxyadenosine; eflornithine; valproic acid; leflunomide; ag 3340; survival rate; prognosis; cancer inhibition; cell proliferation; gene therapy; quality of life; human; clinical trial; meta analysis; human tissue; human cell; adult; review

RN (thalidomide) 50-35-1; (protamine) 11061-43-1, 9007-31-2, 9012-00-4; (vasculotropin) 127464-60-2; (carmustine) 154-93-8; (procarbazine) 366-70-1, 671-16-9; (hydroxyurea) 127-07-1; (teniposide) 29767-20-2; (taxol) 33069-62-4; (topotecan) 119413-54-6, 123948-87-8; (irinotecan) 100286-90-6; (temozolomide)85622-93-1; (2 chlorodeoxyadenosine) 4291-63-8; (eflornithine) 67037-37-0, 70052-12-9; (valproic acid) 1069-66-5, 99-66-1; (leflunomide) 75706-12-6; (ag 3340) 195008-93-6

CN Drug Trade Name: ag 3340

L8 ANSWER 7 OF 40 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
AN 2000:30175900 BIOTECHNO
TI Chemotherapy for high-grade gliomas
AU Galanis E.; Buckner J.
CS E. Galanis, Division of Medical Oncology, Mayo Clinic and Foundation, 200 First Street SW, Rochester, MN 55905, United States.
SO British Journal of Cancer, 2000), 82/8 (1371-1380), 117 reference(s)
CODEN: BJCAAI ISSN: 0007-0920
DT Journal; General Review
CY United Kingdom
LA English
CT *antineoplastic agent; *glioma; 1 (2 chloroethyl) 3 (2,6 dioxo 3 piperidyl) 1 nitrosourea; 6 o benzylguanine; alpha interferon; angiogenesis inhibitor; aziridinylbenzoquinone; carboplatin; carmustine; chlormethine; cisplatin; dacarbazine; fludarabine; fluorouracil; hydroxyurea; irinotecan; lomustine; misonidazole; mitolactol; nalpha [2 [arginylprolyl(4 hydroxyprolyl)glycyl[3 (2 thienyl)alanyl]serylprolylamino] 3 (4 methoxyphenyl)propyl]arginine; nitrosourea; procarbazine; retinoic acid; streptozocin; taxol; temozolomide; teniposide; thalidomide; thiotepa; unindexed drug; vincristine; etoposide; fumagillol chloroacetylcarbamate; leflunomide; blood toxicity; brain disease; cancer adjuvant therapy; cancer grading; cancer immunotherapy; cancer survival; gastrointestinal toxicity; gene therapy; glioblastoma; oligodendroglioma; side effect; thromboembolism; visual impairment; human; clinical trial; phase 2 clinical trial; phase 3 clinical trial; review; priority journal

RN (1 (2 chloroethyl) 3 (2,6 dioxo 3 piperidyl) 1 nitrosourea) 13909-02-9; (6 o benzylguanine) 19916-73-5; (aziridinylbenzoquinone) 526-62-5; (carboplatin) 41575-94-4; (carmustine) 154-93-8; (chlormethine) 51-75-2, 55-86-7, 82905-71-3; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (dacarbazine) 4342-03-4; (fludarabine) 21679-14-1; (fluorouracil) 51-21-8; (hydroxyurea) 127-07-1; (irinotecan) 100286-90-6; (lomustine) 13010-47-4; (misonidazole) 13551-87-6; (mitolactol) 10318-26-0; (nalpha [2 [arginylprolyl(4 hydroxyprolyl)glycyl[3 (2 thienyl)alanyl]serylprolylamino] 3 (4 methoxyphenyl)propyl]arginine) 159768-75-9; (nitrosourea) 13010-20-3; (procarbazine) 366-70-1, 671-16-9; (retinoic acid) 302-79-4; (streptozocin) 18883-66-4; (taxol) 33069-62-4; (temozolomide) 85622-93-1; (teniposide) 29767-20-2; (thalidomide) 50-35-1; (thiotepa) 52-24-4; (vincristine) 57-22-7; (etoposide) 33419-42-0; (fumagillol chloroacetylcarbamate) 129298-91-5; (leflunomide) 75706-12-6

CN Drug Trade Name: vp 16; paclitaxel; vm 26; cpt 11; rmp 7; tnp 470; su 101

L8 ANSWER 8 OF 40 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
AN 1999:29297484 BIOTECHNO
TI New treatment strategies for malignant gliomas
AU Avgeropoulos N.G.; Batchelor T.T.
CS Dr. N.G. Avgeropoulos, Massachusetts General Hospital, Brain Tumor Center, 100 Blossom Street, Boston, MA 02114, United States.
E-mail: batchelor@helix.mgh.harvard.edu
SO Oncologist, 1999), 4/3 (209-224), 126 reference(s)
CODEN: OCOLF6 ISSN: 1083-7159
DT Journal; Article
CY United States
LA English
SL English
AB Although survival in patients with malignant gliomas remains limited, there is renewed optimism with the emergence of novel treatment strategies. Cytotoxic agents such as temozolomide and CPT-11 have shown promising clinical activity. Biological treatments for brain tumors, including antisense oligonucleotides, gene therapy, and angiogenesis inhibitors, are also being evaluated in clinical trials. Delivery strategies have been developed to overcome challenges presented by the blood-brain barrier. These noteworthy treatments, alone or in combination, may ultimately prolong survival and enhance quality of life in this group of patients.

CT *cytotoxic agent; *antisense oligonucleotide; *angiogenesis inhibitor; *angiogenic factor; *anticonvulsive agent; *alkylating agent; *glioblastoma; *astrocytoma; polymer; placebo; carboplatin; temozolomide; irinotecan; topotecan; 9 aminocamptothecin; oxaliplatin; protein kinase c inhibitor; isis 3521; tamoxifen; staurosporine; protein farnesyltransferase inhibitor; cytokine; recombinant alpha2a interferon; carmustine; interleukin 2; thymidine kinase; matrix metalloproteinase inhibitor; marimastat; thalidomide; mannitol; nalpha .cents.2 .cents.arginylprolyl(4 hydroxyprolyl)glycyl.cents.3 (2 thienyl)alanyl!serylprolylamino! 3 (4 methoxyphenyl)propyl!arginine; sensory neuropathy; cancer immunotherapy; lymphokine activated killer cell; t lymphocyte; herpes simplex virus; retrovirus; drug delivery system; cancer survival; gene therapy; blood brain barrier; drug penetration; quality of life; drug structure; drug blood level; drug elimination; drug half life; bone marrow suppression; gastrointestinal toxicity; drug metabolism; fatigue; alopecia; human; nonhuman; clinical trial; oral drug administration; intravenous drug administration; article; priority journal

RN (carboplatin) 41575-94-4; (temozolomide)85622-93-1; (irinotecan) 100286-90-6; (topotecan) 119413-54-6, 123948-87-8; (oxaliplatin) 61825-94-3; (isis 3521) 151879-73-1; (tamoxifen) 10540-29-1; (staurosporine) 62996-74-1; (carmustine) 154-93-8; (interleukin 2) 85898-30-2; (thymidine kinase) 9002-06-6, 9086-73-1; (marimastat) 154039-60-8; (thalidomide)50-35-1; (mannitol) 69-65-8, 87-78-5; (nalpha .cents.2 .cents.arginylprolyl(4 hydroxyprolyl)glycyl.cents.3 (2 thienyl)alanyl!serylprolylamino! 3 (4 methoxyphenyl)propyl!arginine) 159768-75-9

CN Drug Trade Name: isis 3521; rmp 7

L8 ANSWER 9 OF 40 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
AN 1999:29090070 BIOTECHNO
TI Innovative therapies for pediatric brain tumors
AU Rubin J.B.; Kieran M.W.
CS Dr. J.B. Rubin, Dana Farber Cancer Institute, Department of Pediatric Oncology, 44 Binney Street, Boston, MA 02115, United States.
SO Current Opinion in Pediatrics, 1999), 11/1 (39-46), 143 reference(s)
CODEN: COPES0 ISSN: 1040-8703
DT Journal; General Review
CY United States
LA English
SL English
AB Success in the treatment of pediatric brain tumors has lagged behind that of other pediatric cancers. This paper highlights many of the advances that have taken place over the past few years in the surgical,

radiotherapeutic, and chemotherapeutic approaches to central nervous system lesions that we hope will lead to a dramatic improvement in outcome. Innovations in neurosurgical and radiotherapeutic techniques have resulted in decreasing toxicity although substantial improvement in cure rates has not been observed. Many new techniques such as gene therapy, angiogenesis inhibitors, immunotherapy, and others that have not been part of the classic approach to these lesions are now in clinical trials in the hope that they will impact on the survival of these patients. The scientific basis for these new treatment modalities and preliminary clinical results are discussed.

CT *brain tumor; angiogenesis inhibitor; misonidazole; etanidazole; broxuridine; cisplatin; iodine 125; iridium 192; metalloproteinase inhibitor; fumagillol chloroacetylcarbamate; thalidomide; alpha interferon; vitaxin; tenascin; antineoplastic agent; arylbutyric acid derivative; phenylacetic acid; ganglioside gm3; nalpha .cents.2 .cents.arginylprolyl(4 hydroxyprolyl)glycyl.cents.3 (2 thienyl)alanyl!serylprolylamino! 3 (4 methoxyphenyl)propyl!arginine; temozolomide; central nervous system tumor; gene therapy; angiogenesis; immunotherapy; neurosurgery; nuclear magnetic resonance imaging; brachytherapy; dosimetry; proton radiation; stereotaxic surgery; human; infant; child; review; priority journal

RN (misonidazole) 13551-87-6; (etanidazole) 22668-01-5; (broxuridine) 59-14-3; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (iodine 125) 14158-31-7, 22822-81-7; (iridium 192) 14694-69-0; (fumagillol chloroacetylcarbamate) 129298-91-5; (thalidomide)50-35-1; (phenylacetic acid) 103-82-2; (ganglioside gm3) 54827-14-4; (nalpha .cents.2 .cents.arginylprolyl(4 hydroxyprolyl)glycyl.cents.3 (2 thienyl)alanyl!serylprolylamino! 3 (4 methoxyphenyl)propyl!arginine) 159768-75-9; (temozolomide)85622-93-1

CN Drug Trade Name: tnp 470; vitaxin; rmp 7

CO Drug Manufacturer: ixsys, United States; Schering Plough, United States

L8 ANSWER 10 OF 40 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.

AN 1998:28464352 BIOTECHNO

TI New frontiers in therapy of malignant gliomas

AU Puduvalli V.K.; Yung W.K.A.

CS W.K.A. Yung, Department of Neuro-oncology, The University of Texas, M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, United States.

SO FORUM - Trends in Experimental and Clinical Medicine, 1998), 8/3 (261-269), 89 reference(s)
CODEN: FTCME2 ISSN: 1121-8142

DT Journal; General Review

CY Italy

LA English

SL English

AB The prognosis of patients with malignant gliomas remains dismal despite the development of a multidisciplinary approach to their treatment. There is a strong need for novel therapeutic approaches that can make a definite impact in the clinical course of these tumours. Although there have been several advances in diagnostic modalities, surgical techniques and cytotoxic therapies, the development of newer therapies has been hampered by the limited understanding of the factors that determine the biological nature of gliomas. However, inroads are now being made into the understanding of the genetic make-up, biological behaviour and therapeutic response of these tumours, which are expected to pave the way for new modes of treatment. In this article, we review the advances made in the identification of potential targets for glioma therapy and the recent clinical trials utilising biological therapies and newer cytotoxic agents.

CT *glioblastoma; cytotoxic agent; antineoplastic agent; thalidomide; fumigillin; fumagillol chloroacetylcarbamate; angiogenesis inhibitor; angiostatin; thrombocyte factor 4; marimastat; ag 3340; eflornithine; lomustine; procarbazine; vincristine; retinoid; temozolomide; topotecan; irinotecan; unclassified drug; prognosis; disease course; diagnostic procedure; surgical technique; biological therapy; angiogenesis; teratogenicity; side effect; cancer invasion; gene therapy; human; nonhuman; oral drug administration; clinical trial; review

RN (thalidomide) 50-35-1; (fumagillol chloroacetylcarbamate) 129298-91-5; (angiostatin) 172642-30-7, 86090-08-6; (thrombocyte factor 4) 37270-94-3, 69670-74-2; (marimastat) 154039-60-8; (ag 3340) 195008-93-6; (eflornithine) 67037-37-0, 70052-12-9; (lomustine) 13010-47-4; (procarbazine) 366-70-1, 671-16-9; (vincristine) 57-22-7; (temozolomide) 85622-93-1; (topotecan) 119413-54-6, 123948-87-8; (irinotecan) 100286-90-6

CN Drug Trade Name: tnp 470; ag 3340

L8 ANSWER 11 OF 40 CA COPYRIGHT 2003 ACS

AN 133:109949 CA

TI Pharmaceutical compositions for treatment of diseased tissues

IN Lee, Clarence C.; Lee, Feng-Min

PA USA

SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K045-06

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 2, 15

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000040269	A2	20000713	WO 2000-US191	20000105 <--
WO 2000040269	A3	20001130		

W: AU, CA, CN, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRAI US 1999-114906P P 19990105

AB A method to treat diseased tissue is provided where a cytotoxic compd. is administered to a patient in need of treatment in combination with an immunostimulant. Diseased cells and/or infectious microbes/viruses are killed by the cytotoxic compd. in the presence of the immunostimulant. The cell components including cellular contents and cell membrane fragments are presented by the immunostimulant to the host animal as antigens to stimulate the immune responses toward other diseased cells of the same type(s), that either remain in the vicinity or reside in distant tissues or organs. The cytotoxic mol. and immunostimulant are preferably applied locally at high concns., either sequentially or, preferably, simultaneously. For example, the compn. can be administered directly to a target cancer. The compn. can be prepd. in various forms, such as a paste, a time release molded solid shape, a soln., a mixt. with emulsifier, etc. Alternatively, the cytotoxic mol. and immunostimulant are applied in sequence.

ST antitumor immunostimulant antigen formulation local delivery

IT Agrostis alba
Alder (Alnus incana)
Ant (Formicidae)
Artemisia tridentata
Ash (Fraxinus pennsylvanica)
Asteroidea
Bee
Bermuda grass
Birch (Betula alba)
Bromus inermis
Caterpillar
Centipede
Corn
Elm (Ulmus pumila)
Fissurella
Heloderma
Hemiptera
Iva xanthifolia
Jellyfish
Johnson grass (Sorghum halepense)
Juniper (Juniperus scopulorum)
Kentucky bluegrass (Poa pratensis)
Kochia scoparia
Maple (Acer negundo)
Millipede
Mosquito
Oak (Quercus rubra)
Octopus (molluscan common name)
Orchard grass
Poison hemlock
Poison ivy
Poison oak
Poplar (Populus nigra italica)
Ragweed (Ambrosia maritima)
Rye
Scorpaena
Scorpion
Sea anemone
Sea urchin (Echinoidea)
Snake
Spider
Walnut (Juglans nigra)
(allergens of; pharmaceutical compns. for treatment of diseased tissues)

IT Antibiotics
(aminoglycoside; pharmaceutical compns. for treatment of diseased tissues)

IT Antibiotics
(ansamycins; pharmaceutical compns. for treatment of diseased tissues)

IT Nutrients
(anti-; pharmaceutical compns. for treatment of diseased tissues)

IT Macrolides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(antibiotics; pharmaceutical compns. for treatment of diseased tissues)

IT Bacteria (Eubacteria)
Bordetella pertussis
Corynebacterium parvum
Mycobacterium avium
Mycobacterium bovis
Mycobacterium fortuitum
Mycobacterium kansasii
Mycobacterium phlei
Mycobacterium smegmatis
Mycobacterium tuberculosis
Mycobacterium vaccae
Nocardia asteroides
Nocardia rubra
Rhodococcus
(antigens of; pharmaceutical compns. for treatment of diseased tissues)

IT Toxoids
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(botulin; pharmaceutical compns. for treatment of diseased tissues)

IT Proteins, specific or class
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(campath 1H; pharmaceutical compns. for treatment of diseased tissues)

IT Bacteria (Eubacteria)
(cell wall; pharmaceutical compns. for treatment of diseased tissues)

IT Mollusk (Mollusca)
(cone shells, allergens of; pharmaceutical compns. for treatment of diseased tissues)

IT Toxins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(diphtheria; pharmaceutical compns. for treatment of diseased tissues)

IT Toxins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(endotoxins; pharmaceutical compns. for treatment of diseased tissues)

IT Toxins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(exotoxins, immunostimulants; pharmaceutical compns. for treatment of diseased tissues)

IT Toxins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(exotoxins; pharmaceutical compns. for treatment of diseased tissues)

IT Pyrogens
(immunostimulants; pharmaceutical compns. for treatment of diseased tissues)

IT Cytokines
DNA
Mucopolysaccharides, biological studies
RNA
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(immunostimulants; pharmaceutical compns. for treatment of diseased tissues)

IT Drug delivery systems
(local; pharmaceutical compns. for treatment of diseased tissues)

IT Antibiotics
(macrolide; pharmaceutical compns. for treatment of diseased tissues)

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(monoclonal, bispecific murine; pharmaceutical compns. for treatment of diseased tissues)

IT Drug delivery systems
(ointments; pharmaceutical compns. for treatment of diseased tissues)

IT Alkylating agents, biological
Amebicides
Antibiotics
Antitumor agents
Antiviral agents
Cell wall
Chelating agents
Cytotoxic agents
Disinfectants
Fungicides
Immunostimulants

(pharmaceutical compns. for treatment of diseased tissues)
IT Anthracyclines
Antigens
Epoxides
Glycosaminoglycans, biological studies
Interferons
Lipid A
Lipopolysaccharides
Mycolic acids
Mycotoxins
Peptidoglycans
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(pharmaceutical compns. for treatment of diseased tissues)
IT Enzymes, biological studies
Hormones, animal, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. for treatment of diseased tissues)
IT Allergens
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(plant, immunostimulants; pharmaceutical compns. for treatment of diseased tissues)
IT Alkaloids, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(plant-derived immunostimulants; pharmaceutical compns. for treatment of diseased tissues)
IT Proliferation inhibition
(proliferation inhibitors; pharmaceutical compns. for treatment of diseased tissues)
IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(radiolabeled; pharmaceutical compns. for treatment of diseased tissues)
IT Drug delivery systems
(sustained-release; pharmaceutical compns. for treatment of diseased tissues)
IT Toxoids
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(tetanus; pharmaceutical compns. for treatment of diseased tissues)
IT Drug delivery systems
(topical; pharmaceutical compns. for treatment of diseased tissues)
IT Lactams
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(.beta.-, antibiotics; pharmaceutical compns. for treatment of diseased tissues)
IT Antibiotics
(.beta.-lactam; pharmaceutical compns. for treatment of diseased tissues)
IT 62488-57-7, DHAC
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(DHAC; pharmaceutical compns. for treatment of diseased tissues)
IT 9041-38-7D, Teichoic acid, lipo-
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(Lipoteichoic acid; pharmaceutical compns. for treatment of diseased tissues)
IT 14769-73-4, Levamisole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(allergens of; pharmaceutical compns. for treatment of diseased tissues)
IT 50-35-1, Thalidomide 50-76-0, Dactinomycin 50-81-7, Ascorbic acid, biological studies 51-21-8, 5-Fluorouracil 51-79-6, Urethan 52-67-5, Penicillamine 53-19-0, Mitotane 54-42-2, Idoxuridine 54-62-6, Aminopterin 55-86-7, Nitrogen mustard 56-53-1, Diethylstilbestrol 56-75-7D, Amphenicol, derivs. 58-40-2, Prazine 59-14-3, Budr 59-30-3D, Folic acid, analogs 60-00-4, Edta, biological studies 60-54-8D, Tetracycline, derivs. 62-33-9, Calcium disodium edetate 64-02-8, Sodium edetate 64-18-6, Formic acid, biological studies 64-19-7, Acetic acid, biological studies 67-43-6, Pentetic acid 67-63-0, Isopropanol, biological studies 67-68-5, Dmso, biological studies 68-76-8, Triaziquone 69-33-0, Tuberculdin 70-51-9, Deferoxamine 73-03-0, Cordycepin 75-75-2D, Methanesulfonic acid, derivs. 112-24-3 120-73-0D, Purine, analogs 121-76-6 122-79-2, Phenylacetate 127-07-1, Hydroxyurea 127-07-1D, Hydroxyurea, derivs. 139-33-3, Disodium edetate 150-38-9, Trisodium edetate 151-56-4, Aziridine, biological studies 289-95-2D, Pyrimidine, analogs 302-79-4, Tretinoin 304-55-2, Succimer 320-67-2, 5-Azacytidine 366-70-1, Matulane 459-86-9, Mitoguazone 477-30-5, Demecolcine 518-28-5, Podophyllotoxin 569-57-3, Chlorotrianisene 636-47-5, Stallimycin 642-83-1, Aceglatone 645-05-6, Altretamine 671-16-9, Procarbazine 768-94-5, Amantadine 801-52-5, Porfiromycin 1174-11-4, Xenazoic acid 1310-73-2, Sodium hydroxide, biological studies 1402-44-4, Actinomycin F1 1404-00-8D, Mitomycin, derivs. 1508-45-8, Podophyllinic acid 2-ethylhydrazide 1910-68-5, Methisazone 1954-28-5, Etoglucid 2353-33-5 3572-60-9, Amidinomycin 3731-59-7, Moroxydine 3733-81-1, Defosfamide 3819-34-9, Phenamet 3930-19-6, Streptonigrin 4533-39-5, Nitracrine 4803-27-4, Anthramycin 5300-03-8, 9-cis-Retinoic acid 7440-06-4D, Platinum, complexes, biological studies 7647-01-0, Hydrochloric acid, biological studies 7647-17-8, Cesium chloride, biological studies 7664-93-9, Sulfuric acid, biological studies 7761-88-8, Silver nitrate, biological studies 9001-63-2, Lysozyme 9014-02-2, Zinostatin 9015-68-3, Asparaginase 10318-26-0, Mitolactol 11006-77-2, Statolon 11056-06-7D, Bleomycin, derivs. 12111-24-9, Calcium trisodium pentetate 13010-20-3D, Nitrosourea, derivs. 13311-84-7, Flutamide 13392-28-4, Rimantadine 13494-90-1, Gallium nitrate 13665-88-8, Mopidamol 15663-27-1, Cisplatin 18378-89-7, Plicamycin 20537-88-6, Amifostine 20830-81-3, Daunorubicin 21416-67-1, Razoxane 22668-01-5, Radinyl 23214-92-8, Doxorubicin 24967-93-9, Chondroitin sulfate A 26657-95-4, Dipalmitoylglycerol 26833-87-4, Homoharringtonine 27314-97-2, Tirapazamine 27762-78-3, Kethoxal 27778-66-1, Tenuazonic acid 29767-20-2, Teniposide 33069-62-4, Paclitaxel 33419-42-0, Etoposide 36703-88-5, Isoprinosine 36791-04-5, Ribavirin 38819-10-2, Guanine arabinoside 39389-47-4, Diatmycin 41992-23-8, Spirogermanium 50264-69-2, Lonidamine 51264-14-3, Amsacrine 52205-73-9, Estramustine phosphate sodium 53678-77-6, Muramyl dipeptide 53783-83-8, Tromantadine 53910-25-1, Pentostatin 56741-95-8, Bropirimine 57998-68-2, Diaziquone 58066-85-6, Miltefosine 58337-35-2, Elliptinium acetate 58957-92-9, Idarubicin 61825-94-3, Oxaliplatin 63585-09-1, Foscarnet sodium 63612-50-0, Nilutamide 65271-80-9, Mitoxantrone 65646-68-6, Fenretinide 66676-88-8D, Aclacinomycin, derivs. 70052-12-9, Eflornithine 72732-56-0, Piritrexim 74853-75-1 74913-06-7D, Chromomycin, derivs. 75706-12-6, SU101 78186-34-2, Bisantrene 80738-43-8D, Lincosamide, derivs. 82413-20-5, Droloxifene 82952-64-5, Trimetrexate glucuronate 83314-01-6, Bryostatin 1 84088-42-6, Linomide 85622-93-1, Temozolomide 89778-26-7, Toremifene 95058-81-4, Gemcitabine 96389-68-3, Crisnatol 97682-44-5, Irinotecan 97919-22-7 98631-95-9, Sobuzoxane 98930-34-8 107868-30-4, Exemestane 110042-95-0, Acemannan 110314-48-2, Adozelesin 112809-51-5, Letrozole 114977-28-5, Docetaxel 115575-11-6, Liarozole 116057-75-1, Idoxifene 120511-73-1, Anastrozole 121181-53-1, Filgrastim 123948-87-8, Topotecan 125317-39-7, Navelbine 126268-81-3, CI-980 127779-20-8, Saquinavir 129618-40-2, Nevirapine 129655-21-6, Bizelesin 133432-71-0, Peldesine 135467-16-2, Octreotide pamoate 136817-59-9, Delavirdine 144849-63-8, Bismafide 150378-17-9, Indinavir 154361-50-9, Capecitabine 155213-67-5, Ritonavir 159768-75-9, RMP-7 159997-94-1, VX-710 282102-49-2 282102-50-5 282527-39-3 282527-40-6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(pharmaceutical compns. for treatment of diseased tissues)

L8 ANSWER 12 OF 40 CA COPYRIGHT 2003 ACS
AN 131:346535 CA
TI Use of neomycin for treating angiogenesis-related diseases
IN Hu, Guo-Fu; Vallee, Bert L.
PA The Endowment for Research In Human Biology, Inc., USA
SO PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-37
CC 1-8 (Pharmacology)
Section cross-reference(s): 2, 15, 63
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	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9958126	A1	19991118	WO 1999-US10269	19990511	<--
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	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
	CA 2331620	AA	19991118	CA 1999-2331620	19990511	<--
	AU 9939804	A1	19991129	AU 1999-39804	19990511	<--
	EP 1083896	A1	20010321	EP 1999-922915	19990511	
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
	US 6482802	B1	20021119	US 2000-700436	20001109	
PRAI	US 1998-84921P	P	19980511			
	WO 1999-US10269	W	19990511			

AB The present invention is directed to using neomycin or an analog thereof as a therapeutic agent to treat angiogenesis-related diseases, which are characterized by excessive, undesired or inappropriate angiogenesis or proliferation of endothelial cells. The present invention is also directed to pharmaceutical compns. comprising: (a) neomycin or an analog and, optionally, (b) another anti-angiogenic agent or an anti-neoplastic agent. The present invention is further directed to a method for screening neomycin analogs having anti-angiogenic activity. A preferred embodiment of the invention relates to using neomycin to treat subjects having such diseases. A dose of 20 ng neomycin/embryo or higher completely inhibited angiogenin-induced angiogenesis in the chorioallantoic membrane (CAM) assay. Neomycin inhibits angiogenin-induced angiogenesis mainly through inhibition of nuclear translocation of angiogenin.
ST neomycin analog angiogenesis inhibition antitumor
IT Eye, disease
(Best's disease; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Intestine, disease
(Crohn's; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Eye, disease
(Eales' disease; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(Ewing's sarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(Kaposi's sarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Bone, disease
(Paget's; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Lymphoproliferative disorders
(Waldenstrom's macroglobulinemia; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Sarcoidosis
(Wegener's; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(Wilms' tumor; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Kidney, neoplasm
(Wilms', inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Nerve, neoplasm
(acoustic neuroma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(acoustic neuroma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(acute lymphocytic leukemia; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(adenocarcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antibiotics
(aminoglycoside; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Artery, disease
(arteritis; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Astrocyte
(astrocytoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(astrocytoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Ulcer
(bacterial and fungal; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Skin, neoplasm
(basal cell carcinoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(basal cell carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(bile duct carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Biliary tract
(bile duct, carcinoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(bladder carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(bronchi carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Bladder
Bladder
Bronchi
Sebaceous gland
Sebaceous gland
(carcinoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Lung, neoplasm
(carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Artery, disease
(carotid, occlusion; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Uterus, neoplasm
(cervix, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(cervix; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Burn
(chem.; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Cartilage
(chondrosarcoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(chondrosarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Notochord
(chordoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(chordoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Chorion
(choriocarcinoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(choriocarcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(colon carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Intestine, neoplasm
(colon, carcinoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Drug delivery systems
(compns. of neomycin and analogs for treatment of angiogenesis-related diseases)
IT Eye, disease
(contact lens overwear; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Transplant rejection
(corneal; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Pituitary gland, anterior lobe
(craniopharyngioma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(craniopharyngioma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Ovary, neoplasm
(cystadenocarcinoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(cystadenocarcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Eye, disease
(diabetic retinopathy; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(embryonal carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Blood vessel
(endothelium; neomycin and analogs as inhibitors of angiogenesis in endothelium and chorioallantoic membrane)
IT Brain, neoplasm
(ependymoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(ependymoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(epithelial carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(fibrosarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Neuroglia
(glioma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(glioma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Immunoglobulins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(heavy chain disease inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(hemangioblastoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Blood vessel, neoplasm
(hemangioma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(hemangioma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Blood vessel, neoplasm
(hemangiosarcoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(hemangiosarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Liver, neoplasm
(hepatoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(hepatoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Capillary vessel
(hereditary hemorrhagic telangiectasia; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Human herpesvirus 3
(herpes zoster from, infections; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Human herpesvirus
Mycobacterium
(infections; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Ovary, neoplasm
Pancreas, neoplasm
Testis, neoplasm
(inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Biological transport
(intracellular; neomycin and analogs are inhibitors of nuclear translocation of angiogenic factors for treatment of angiogenesis-related diseases)
IT Eye, disease
(keratitis; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Eye, disease
(keratoconjunctivitis, epidemic; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(leiomyosarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(leukemia, acute myelocytic; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(leukemia, chronic; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Lipids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(lipid degeneration inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Adipose tissue, neoplasm
(liposarcoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(liposarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(lymphangioendotheliosarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Lymphatic system
(lymphangiosarcoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(lymphangiosarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(lymphoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Eye, disease
(macula, degeneration, Stargardt's disease; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Eye, disease
(macula, degeneration; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Brain, neoplasm
Brain, neoplasm
(medulloblastoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(medulloblastoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(melanoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Meninges
Meninges
(meningioma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(meningioma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Mesothelium
(mesothelioma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Erythema
(multiforme; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(multiple myeloma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(myxosarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Angiogenic factors
Hepatocyte growth factor
Interleukin 8
Platelet-derived growth factors
Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(neomycin and analogs are inhibitors of nuclear translocation of angiogenic factors for treatment of angiogenesis-related diseases)
IT Chorioallantois
(neomycin and analogs as inhibitors of angiogenesis in endothelium and chorioallantoic membrane)
IT Angiogenesis inhibitors
Anti-AIDS agents
Antibacterial agents
Antirheumatic agents
Antitumor agents
Antiulcer agents
Antiviral agents
Behcet's syndrome
Cytotoxic agents
Fungicides
Lyme disease

Polycythemia vera
Protein sequences
Protozoacides
Psoriasis
Sarcoidosis
Sickle cell anemia
Sjogren's syndrome
Syphilis
(neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Anthracyclines
Interleukin 12
Interleukin 2
Peptides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Notochord
(neoplasm, chordoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Mammary gland
Prostate gland
Sweat gland
Sweat gland
(neoplasm, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Glaucoma (disease)
(neovascular; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Nerve, neoplasm
Nerve, neoplasm
(neuroblastoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(neuroblastoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Schwann cell
(neurofibroma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(neurofibroma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Artery, disease
Vein
(occlusion; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Neuroglia
(oligodendroglioma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(oligodendroglioma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(osteogenic sarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(ovary; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(pancreas; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(papillary adenocarcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(papillary carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Eye, disease
(pars planitis; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Eye, disease
(periretinal proliferation; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(pinealoma inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Pineal gland
(pinealoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Placental hormones
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(placenta-derived mitogenic factors; neomycin and analogs are inhibitors of nuclear translocation of angiogenic factors for treatment of angiogenesis-related diseases)

IT Eye, disease
(presumed ocular histoplasmosis; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Proliferation inhibition
(proliferation inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Skin, neoplasm
(pseudoxanthoma elasticum; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(pyogenic granuloma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Kidney, neoplasm
(renal cell carcinoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(renal cell carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Eye, disease
(retinitis; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Eye, neoplasm
(retinoblastoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(retinoblastoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Eye, disease
(retinopathy, detachment, chronic; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Eye, disease
(retrolental fibroplasia; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(rhabdomyosarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Skin, disease
(rosacea; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Eye, disease
(scleritis; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Drug screening
(screening of neomycin and analogs for treatment of angiogenesis-related diseases)

IT Antitumor agents
(sebaceous gland carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Testis, neoplasm
(seminoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(seminoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Lung, neoplasm
(small-cell carcinoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(squamous cell carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(sweat gland; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(synovial membrane tumor inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Lupus erythematosus
(systemic; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(testis; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Toxoplasma gondii
(toxoplasmosis from; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(trachoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Injury
(trauma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Synovial membrane
(tumors, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Intestine, disease
(ulcerative colitis; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Eye, disease
(uveitis, chronic; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.alpha.-; neomycin and analogs are inhibitors of nuclear translocation of angiogenic factors for treatment of angiogenesis-related diseases)

IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.alpha.; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.-; neomycin and analogs are inhibitors of nuclear translocation of angiogenic factors for treatment of angiogenesis-related diseases)

IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta.; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.gamma.; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT 11103-57-4, Vitamin A
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(deficiency; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT 9001-86-9, Phospholipase C
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; neomycin and analogs as inhibitors of phospholipase C for treatment of angiogenesis-related diseases)

IT 61912-98-9, Insulin-like growth factor 62229-50-9, Epidermal growth factor 65154-06-5, Platelet activating factor 97950-81-7, Angiogenin (human) 106096-92-8, Acidic fibroblast growth factor 106096-93-9, Basic fibroblast growth factor 127464-60-2, Vascular endothelial growth factor 143011-72-7, Granulocyte colony-stimulating factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(neomycin and analogs are inhibitors of nuclear translocation of angiogenic factors for treatment of angiogenesis-related diseases)

IT 66-86-4, Neomycin C 119-04-0, Neomycin B 1404-04-2, Neomycin 2037-48-1, 2-Deoxystreptamine 3947-65-7, Neomycin A 7542-37-2, Paromomycin 11111-23-2, Lividomycin 25546-65-0, Ribostamycin 34051-04-2, Nebramine 35025-95-7, Gentamine C1a 50474-67-4, Xylostasin 51053-37-3, Gentamine C1 51053-38-4, Gentamine C2 84420-34-8, Paromomycin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neomycin and analogs for treatment of angiogenesis-related diseases)

IT 50-18-0, Cyclophosphamide 50-35-1, Thalidomide 50-44-2, 6-Mercaptopurine 50-76-0, Dactinomycin 50-91-9, Floxuridine 51-18-3, Triethylenemelamine 51-21-8, Fluorouracil 51-75-2, Mechlorethamine 51-79-6, Urethane 52-24-4, Triethylenethiophosphoramide 52-67-5, D-Penicillamine 53-19-0, Mitotane 53-79-2, Puromycin 54-25-1, 6-Azauridine 54-91-1, Pipobroman 55-98-1, Busulfan 57-22-7, Vincristine 58-05-9, Polinic acid 58-19-5, Dromostanolone 59-05-2, Methotrexate 66-75-1, Uracil mustard 68-76-8, Triaziquone 69-33-0, Tubercidin 84-16-2, Hexestrol 89-38-3, Pteropterin 115-02-6, Azaserine 125-84-8, Aminoglutethimide 127-07-1, Hydroxyurea 147-94-4, Cytarabine 148-82-3, Melphalan 151-56-4D, Aziridine, derivs., biological studies 154-42-7, Thioguanine 154-93-8, Carmustine 157-03-9, 6-Diazo-5-oxo-L-norleucine 302-22-7, Chlormadinone acetate 302-49-8, Uredepa 302-70-5, Mechlorethamine oxide hydrochloride 305-03-3, Chlorambucil 320-67-2, Azacitidine 362-07-2, 2-Methoxyestradiol 459-86-9, Mitoguazone 477-30-5, Demecolcine 488-41-5, Mitobronitol 494-03-1, Chlornaphazine 520-85-4, Medroxyprogesterone 522-40-7, Fosfestrol 545-55-1, Triethylenephosphoramide 555-77-1, 2,2',2''-Trichlorotriethylamine 566-48-3, Formestane 576-68-1, Mannomustine 595-33-5, Megestrol acetate 642-83-1, Aceglatone 645-05-6, Altretamine 801-52-5, Porfiromycin 865-21-4, Vinblastine 968-93-4, Testolactone 1402-44-4, Actinomycin F1 1403-28-7, Carzinophilin 1404-00-8, Mitomycin 1404-15-5, Nogalamycin 1508-45-8, Podophyllinic acid 2-ethyl hydrazide 1661-29-6, Meturedepa 1936-40-9, Novembichin 1954-28-5, Etoglucid 1980-45-6, Benzodepa 2363-58-8, Epitiostanol 2608-24-4, Piposulfan 2998-57-4, Estramustine 3094-09-5, Doxifluridine 3546-10-9, Phenesterine 3733-81-1, Defosfamide 3778-73-2, Ifosfamide 3819-34-9,

Phenamet 3930-19-6, Streptonigrin 4291-63-8, Cladribine 4342-03-4, Dacarbazine 4533-39-5, Nitracrine 4803-27-4, Anthramycin 5581-52-2, Thiamiprine 5633-18-1, Melengestrol 8052-16-2, Cactinomycin 9014-02-2, Zinostatin 9015-68-3, L-Asparaginase 9042-14-2, Dextran sulfate 10318-26-0, Mitolactol 10540-29-1, Tamoxifen 11006-70-5, Olivomycin 11056-06-7, Bleomycin 13010-47-4, Lomustine 13311-84-7, Flutamide 13425-98-4, Improsulfan 13494-90-1, Gallium nitrate 13647-35-3, Trilostane 13665-88-8, Mopidamol 15663-27-1, Cisplatin 17021-26-0, Calusterone 17902-23-7, Tegafur 18378-89-7, Plicamycin 18883-66-4, Streptozocin 20830-81-3, Daunorubicin 21362-69-6, Mepitiostane 21416-67-1, Razoxane 21679-14-1, Fludarabine 22006-84-4, Denopterin 22089-22-1, Trofosfamide 23110-15-8, Fumagillin 23214-92-8, Doxorubicin 24279-91-2, Carboquone 24280-93-1, Mycophenolic acid 28014-46-2, Polyestradiol phosphate 29069-24-7, Prednimustine 29767-20-2, Teniposide 31698-14-3, Ancitabine 33069-62-4, Paclitaxel 33419-42-0, Etoposide 37270-94-3, Platelet factor 4 37339-90-5, Lentinan 41575-94-4, Carboplatin 41992-23-8, Spirogermanium 42471-28-3, Nimustine 50264-69-2, Lonidamine 50935-04-1, Carubicin 51264-14-3, Amsacrine 52128-35-5, Trimetrexate 53123-88-9, Rapamycin 53643-48-4, Vindesine 53714-56-0, Leuprolide 53910-25-1, Pentostatin 54083-22-6, Zorubicin 54749-90-5, Chlorozotocin 55726-47-1, Enocitabine 56420-45-2, Epirubicin 57773-63-4, Triptorelin 57982-77-1, Buserelin 57998-68-2, Diaziquone 58066-85-6, Miltefosine 58337-35-2, Elliptinium acetate 58957-92-9, Idarubicin 58970-76-6, Ubenimex 58994-96-0, Ranimustine 61163-28-8, .beta.-1,3-Glucan sulfate 61422-45-5, Carmofur 61825-94-3, Oxaliplatin 62435-42-1, Perfosfamide 63612-50-0, Nilutamide 64431-69-2, Aclacinomycin S 65271-80-9, Mitoxanthrone 65646-68-6, Fenretinide 65807-02-5, Goserelin 68247-85-8, Peplomycin 70052-12-9, Eflornithine 70563-58-5, Herbimycin A 71628-96-1, Menogaril 72496-41-4, Pirarubicin 72732-56-0, Piritrexim 74913-06-7, Chromomycin 78186-34-2, Bisantrene 80576-83-6, Edatrexate 82413-20-5, Droloxifene 84088-42-6, Roquinimex 85622-93-1, Temozolomide 86090-08-6, Angiostatin 87806-31-3, Porfimer sodium 89149-10-0, 15-Deoxyspergualin 89778-26-7, Toremifene 90357-06-5, Bicalutamide 92118-27-9, Fotemustine 95058-81-4, Gemcitabine 98631-95-9, Sobuzoxane 99519-84-3, CAI 100286-90-6 102676-47-1, Fadrozole 103775-75-3, Miboplatin 110690-43-2, Emitefur 112809-51-5, Letrozole 112887-68-0, Tomudex 114977-28-5, Docetaxel 120511-73-1, Anastrozole 123948-87-8, Topotecan 126509-46-4, Eponemycin 126595-07-1, Propagermanium 129298-91-5, AGM 1470 130370-60-4, Batimastat 142298-75-7, Ribonuclease inhibitor 154039-60-8, Marimastat 187888-07-9, Endostatin 188417-67-6, CM 101 196858-78-3 197850-48-9 197850-49-0 250331-65-8 250593-25-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Waksman; US 2799620 A 1957 CA

L8 ANSWER 13 OF 40 CANCERLIT
AN 2001075767 CANCERLIT
DN 21075767 PubMed ID: 11204670
TI New approaches in the treatment of metastatic melanoma: thalidomide and temozolomide.
AU Hwu W J
CS Memorial Sloan-Kettering Cancer Center, New York, New York, USA.
SO ONCOLOGY, (2000 Dec) 14 (12 Suppl 13) 25-8. Ref: 16
Journal code: 8712059. ISSN: 0890-9091.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2001192567
EM 200104
ED Entered STN: 20010515
Last Updated on STN: 20010515
AB Although melanoma is a relatively chemoresistant malignancy, systemic chemotherapy remains the primary treatment for metastatic melanoma. The observation of vasculogenic mimicry in aggressive melanoma has prompted investigation into using an antiangiogenic agent to enhance the antitumor activity of chemotherapy in metastatic melanoma. Thalidomide (Thalomid) exhibits antiangiogenic activity and other biological modulatory effects that may provide additive or synergistic antitumor effects when given concurrently with chemotherapy. A phase I/II study of thalidomide and temozolomide in the treatment of metastatic melanoma is in progress. Preliminary results of this combination therapy have shown significant antitumor activity, including some striking responses in brain metastases.
CT Check Tags: Case Report; Female; Human; Male
Adult
*Angiogenesis Inhibitors: TU, therapeutic use
*Antineoplastic Agents, Alkylating: TU, therapeutic use
*Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use
Clinical Trials, Phase I
Clinical Trials, Phase II
*Dacarbazine: AA, analogs & derivatives
*Dacarbazine: TU, therapeutic use
*Melanoma: DT, drug therapy
Middle Age
Neoplasm Metastasis
*Thalidomide: TU, therapeutic use
RN 4342-03-4 (Dacarbazine); 50-35-1 (Thalidomide); 85622-93-1 (temozolomide)
CN 0 (Angiogenesis Inhibitors); 0 (Antineoplastic Agents, Alkylating); 0 (Antineoplastic Combined Chemotherapy Protocols)

L8 ANSWER 14 OF 40 CANCERLIT
AN 1999259140 CANCERLIT
DN 99259140 PubMed ID: 10328588
TI New chemotherapy options for the treatment of malignant gliomas.
AU Burton E; Prados M
CS University of California, San Francisco, Department of Neurosurgery, USA.
NC CA09291 (NCI)
CA13525 (NCI)
SO CURRENT OPINION IN ONCOLOGY, (1999 May) 11 (3) 157-61. Ref: 24
Journal code: 9007265. ISSN: 1040-8746.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals; AIDS
OS MEDLINE 1999259140
EM 199906
ED Entered STN: 19990813
Last Updated on STN: 19990813
AB Chemotherapy remains part of the treatment triad that includes surgery and radiation therapy for the management of malignant gliomas. In recent years there has been an increased understanding of the molecular pathways of malignant transformation. Based on this research, new drugs have been evaluated, with specific cellular targets in mind that can be modified or inhibited. Many of these agents are now being tested in phase I and II clinical trials and have shown some promising results. Clearly, not all patients with malignant gliomas respond equally to chemotherapy. Recent evidence suggests that certain molecular markers may predict chemosensitivity in some tumor types, particularly anaplastic oligodendroglioma. This article reviews recent trends in the use of chemotherapy and clinical trials of new therapies for adults with malignant gliomas.
CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
Adult
*Antineoplastic Agents: TU, therapeutic use
*Brain Neoplasms: DT, drug therapy
Brain Neoplasms: PP, physiopathology
Camptothecin: AA, analogs & derivatives
Camptothecin: TU, therapeutic use
Clinical Trials
Dacarbazine: AA, analogs & derivatives
Dacarbazine: TU, therapeutic use
Enzyme Inhibitors: TU, therapeutic use
*Glioma: DT, drug therapy
Glioma: PP, physiopathology
Neovascularization, Pathologic: PC, prevention & control
Oligodendroglioma: DT, drug therapy
Oligodendroglioma: GE, genetics
Protease Inhibitors: TU, therapeutic use
Signal Transduction: PH, physiology
Thalidomide: TU, therapeutic use
RN 100286-90-6 (irinotecan); 4342-03-4 (Dacarbazine); 50-35-1 (Thalidomide); 7689-03-4 (Camptothecin); 85622-93-1 (temozolomide)
CN 0 (Antineoplastic Agents); 0 (Enzyme Inhibitors); 0 (Protease Inhibitors)

L8 ANSWER 15 OF 40 CAPLUS COPYRIGHT 2003 ACS
AN 2000:475560 CAPLUS
DN 133:109949
TI Pharmaceutical compositions for treatment of diseased tissues
IN Lee, Clarence C.; Lee, Feng-Min
PA USA
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K045-06
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 2, 15
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000040269	A2	20000713	WO 2000-US191	20000105 <--
	WO 2000040269	A3	20001130		

W: AU, CA, CN, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRAI US 1999-114906P P 19990105
AB A method to treat diseased tissue is provided where a cytotoxic compd. is administered to a patient in need of treatment in combination with an immunostimulant. Diseased cells and/or infectious microbes/viruses are killed by the cytotoxic compd. in the presence of the immunostimulant. The cell components including cellular contents and cell membrane fragments are presented by the immunostimulant to the host animal as antigens to stimulate the immune responses toward other diseased cells of the same type(s), that either remain in the vicinity or reside in distant tissues or organs. The cytotoxic mol. and immunostimulant are preferably applied locally at high concns., either sequentially or, preferably, simultaneously. For example, the compn. can be administered directly to a target cancer. The compn. can be prepd. in various forms, such as a paste, a time release molded solid shape, a soln., a mixt. with emulsifier, etc. Alternatively, the cytotoxic mol. and immunostimulant are applied in sequence.
ST antitumor immunostimulant antigen formulation local delivery
IT Agrostis alba
Alder (Alnus incana)
Ant (Formicidae)
Artemisia tridentata
Ash (Fraxinus pennsylvanica)
Asteroidea
Bee
Bermuda grass
Birch (Betula alba)
Bromus inermis
Caterpillar
Centipede
Corn
Elm (Ulmus pumila)
Fissurella
Heloderma
Hemiptera
Iva xanthifolia
Jellyfish
Johnson grass (Sorghum halepense)
Juniper (Juniperus scopulorum)
Kentucky bluegrass (Poa pratensis)
Kochia scoparia
Maple (Acer negundo)
Millipede
Mosquito
Oak (Quercus rubra)
Octopus (molluscan common name)
Orchard grass
Poison hemlock
Poison ivy
Poison oak
Poplar (Populus nigra italica)
Ragweed (Ambrosia maritima)
Rye
Scorpaena
Scorpion
Sea anemone
Sea urchin (Echinoidea)
Snake
Spider
Walnut (Juglans nigra)
(allergens of; pharmaceutical compns. for treatment of diseased tissues)
IT Antibiotics
(aminoglycoside; pharmaceutical compns. for treatment of diseased tissues)
IT Antibiotics
(ansamycins; pharmaceutical compns. for treatment of diseased tissues)
IT Nutrients
(anti-; pharmaceutical compns. for treatment of diseased tissues)
IT Macrolides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(antibiotics; pharmaceutical compns. for treatment of diseased tissues)
IT Bacteria (Eubacteria)
Bordetella pertussis
Corynebacterium parvum
Mycobacterium avium
Mycobacterium bovis

Mycobacterium fortuitum
Mycobacterium kansasii
Mycobacterium phlei
Mycobacterium smegmatis
Mycobacterium tuberculosis
Mycobacterium vaccae
Nocardia asteroides
Nocardia rubra
Rhodococcus
(antigens of; pharmaceutical compns. for treatment of diseased tissues)

IT Toxoids
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(botulin; pharmaceutical compns. for treatment of diseased tissues)

IT Proteins, specific or class
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(campath 1H; pharmaceutical compns. for treatment of diseased tissues)

IT Bacteria (Eubacteria)
(cell wall; pharmaceutical compns. for treatment of diseased tissues)

IT Mollusk (Mollusca)
(cone shells, allergens of; pharmaceutical compns. for treatment of diseased tissues)

IT Toxins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(diphtheria; pharmaceutical compns. for treatment of diseased tissues)

IT Toxins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(endotoxins; pharmaceutical compns. for treatment of diseased tissues)

IT Toxins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(exotoxins, immunostimulants; pharmaceutical compns. for treatment of diseased tissues)

IT Toxins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(exotoxins; pharmaceutical compns. for treatment of diseased tissues)

IT Pyrogens
(immunostimulants; pharmaceutical compns. for treatment of diseased tissues)

IT Cytokines
DNA
Mucopolysaccharides, biological studies
RNA
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(immunostimulants; pharmaceutical compns. for treatment of diseased tissues)

IT Drug delivery systems
(local; pharmaceutical compns. for treatment of diseased tissues)

IT Antibiotics
(macrolide; pharmaceutical compns. for treatment of diseased tissues)

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(monoclonal, biospecific murine; pharmaceutical compns. for treatment of diseased tissues)

IT Drug delivery systems
(ointments; pharmaceutical compns. for treatment of diseased tissues)

IT Alkylating agents, biological
Amebicides
Antibiotics
Antitumor agents
Antiviral agents
Cell wall
Chelating agents
Cytotoxic agents
Disinfectants
Fungicides
Immunostimulants
(pharmaceutical compns. for treatment of diseased tissues)

IT Anthracyclines
Antigens
Epoxides
Glycosaminoglycans, biological studies
Interferons
Lipid A
Lipopolysaccharides
Mycolic acids
Mycotoxins
Peptidoglycans
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(pharmaceutical compns. for treatment of diseased tissues)

IT Enzymes, biological studies
Hormones, animal, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. for treatment of diseased tissues)

IT Allergens
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(plant, immunostimulants; pharmaceutical compns. for treatment of diseased tissues)

IT Alkaloids, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(plant-derived immunostimulants; pharmaceutical compns. for treatment of diseased tissues)

IT Proliferation inhibition
(proliferation inhibitors; pharmaceutical compns. for treatment of diseased tissues)

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(radiolabeled; pharmaceutical compns. for treatment of diseased tissues)

IT Drug delivery systems
(sustained-release; pharmaceutical compns. for treatment of diseased tissues)

IT Toxoids
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(tetanus; pharmaceutical compns. for treatment of diseased tissues)

IT Drug delivery systems
(topical; pharmaceutical compns. for treatment of diseased tissues)

IT Lactams
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(.beta.-, antibiotics; pharmaceutical compns. for treatment of diseased tissues)

IT Antibiotics
(.beta.-lactam; pharmaceutical compns. for treatment of diseased tissues)

IT 62488-57-7, DHAC
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(DHAC; pharmaceutical compns. for treatment of diseased tissues)

IT 9041-38-7D, Teichoic acid, lipo-
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(Lipoteichoic acid; pharmaceutical compns. for treatment of diseased tissues)

IT 14769-73-4, Levamisole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(allergens of; pharmaceutical compns. for treatment of diseased tissues)

IT 50-35-1, Thalidomide 50-76-0, Dactinomycin 50-81-7, Ascorbic acid, biological studies 51-21-8, 5-Fluorouracil 51-79-6, Urethan 52-67-5, Penicillamine 53-19-0, Mitotane 54-42-2, Idoxuridine 54-62-6, Aminopterin 55-86-7, Nitrogen mustard 56-53-1, Diethylstilbestrol 56-75-7D, Amphenicol, derivs. 58-40-2, Prazine 59-14-3, Budr 59-30-3D, Folic acid, analogs 60-00-4, Edta, biological studies 60-54-8D, Tetracycline, derivs. 62-33-9, Calcium disodium edetate 64-02-8, Sodium edetate 64-18-6, Formic acid, biological studies 64-19-7, Acetic acid, biological studies 67-43-6, Pentetic acid 67-63-0, Isopropanol, biological studies 67-68-5, Dmso, biological studies 68-76-8, Triaziquone 69-33-0, Tubercidin 70-51-9, Deferoxamine 73-03-0, Cordycepin 75-75-2D, Methanesulfonic acid, derivs. 112-24-3 120-73-0D, Purine, analogs 121-76-6 122-79-2, Phenylacetate 127-07-1, Hydroxyurea 127-07-1D, Hydroxyurea, derivs. 139-33-3, Disodium edetate 150-38-9, Trisodium edetate 151-56-4, Aziridine, biological studies 289-95-2D, Pyrimidine, analogs 302-79-4, Tretinoin 304-55-2, Succimer 320-67-2, 5-Azacytidine 366-70-1, Matulane 459-86-9, Mitoguazone 477-30-5, Demecolcine 518-28-5, Podophyllotoxin 569-57-3, Chlorotrianisene 636-47-5, Stallimycin 642-83-1, Aceglatone 645-05-6, Altretamine 671-16-9, Procarbazine 768-94-5, Amantadine 801-52-5, Porfiromycin 1174-11-4, Xenazoic acid 1310-73-2, Sodium hydroxide, biological studies 1402-44-4, Actinomycin F1 1404-00-8D, Mitomycin, derivs. 1508-45-8, Podophyllinic acid 2-ethylhydrazide 1910-68-5, Methisazone 1954-28-5, Etoglucid 2353-33-5 3572-60-9, Amidinomycin 3731-59-7, Moroxydine 3733-81-1, Defosfamide 3819-34-9, Phenamet 3930-19-6, Streptonigrin 4533-39-5, Nitracrine 4803-27-4, Anthramycin 5300-03-8, 9-cis-Retinoic acid 7440-06-4D, Platinum, complexes, biological studies 7647-01-0, Hydrochloric acid, biological studies 7647-17-8, Cesium chloride, biological studies 7664-93-9, Sulfuric acid, biological studies 7761-88-8, Silver nitrate, biological studies 9001-63-2, Lysozyme 9014-02-2, Zinostatin 9015-68-3, Asparaginase 10318-26-0, Mitolactol 11006-77-2, Statolon 11056-06-7D, Bleomycin, derivs. 12111-24-9, Calcium trisodium pentetate 13010-20-3D, Nitrosourea, derivs. 13311-84-7, Flutamide 13392-28-4, Rimantadine 13494-90-1, Gallium nitrate 13665-88-8, Mopidamol 15663-27-1, Cisplatin 18378-89-7, Plicamycin 20537-88-6, Amifostine 20830-81-3, Daunorubicin 21416-67-1, Razoxane 22668-01-5, Radinyl 23214-92-8, Doxorubicin 24967-93-9, Chondroitin sulfate A 26657-95-4, Dipalmitoylglycerol 26833-87-4, Homoharringtonine 27314-97-2, Tirapazamine 27762-78-3, Kethoxal 27778-66-1, Tenuazonic acid 29767-20-2, Teniposide 33069-62-4, Paclitaxel 33419-42-0, Etoposide 36703-88-5, Isoprinosine 36791-04-5, Ribavirin 38819-10-2, Guanine arabinoside 39389-47-4, Distamycin 41992-23-8, Spirogermanium 50264-69-2, Lonidamine 51264-14-3, Amsacrine 52205-73-9, Estramustine phosphate sodium 53678-77-6, Muramyl dipeptide 53783-83-8, Tromantadine 53910-25-1, Pentostatin 56741-95-8, Bropirimine 57998-68-2, Diaziquone 58066-85-6, Miltefosine 58337-35-2, Elliptinium acetate 58957-92-9, Idarubicin 61825-94-3, Oxaliplatin 63585-09-1, Foscarnet sodium 63612-50-0, Nilutamide 65271-80-9, Mitoxantrone 65646-68-6, Fenretinide 66676-88-8D, Aclacinomycin, derivs. 70052-12-9, Eflornithine 72732-56-0, Piritrexim 74853-75-1 74913-06-7D, Chromomycin, derivs. 75706-12-6, SU101 78186-34-2, Bisantrene 80738-43-8D, Lincosamide, derivs. 82413-20-5, Droloxifene 82952-64-5, Trimetrexate glucuronate 83314-01-6, Bryostatin 1 84088-42-6, Linomide 85622-93-1, Temozolomide 89778-26-7, Toremifene 95058-81-4, Gemcitabine 96389-68-3, Crisnatol 97682-44-5, Irinotecan 97919-22-7 98631-95-9, Sobuzoxane 98930-34-8 107868-30-4, Exemestane 110042-95-0, Acemannan 110314-48-2, Adozelesin 112809-51-5, Letrozole 114977-28-5, Docetaxel 115575-11-6, Liarozole 116057-75-1, Idoxifene 120511-73-1, Anastrozole 121181-53-1, Filgrastim 123948-87-8, Topotecan 125317-39-7, Navelbine 126268-81-3, CI-980 127779-20-8, Saquinavir 129618-40-2, Nevirapine 129655-21-6, Bizelesin 133432-71-0, Peldesine 135467-16-2, Octreotide pamoate 136817-59-9, Delavirdine 144849-63-8, Bisnafide 150378-17-9, Indinavir 154361-50-9, Capecitabine 155213-67-5, Ritonavir 159768-75-9, RMP-7 159997-94-1, VX-710 282102-49-2 282102-50-5 282527-39-3 282527-40-6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(pharmaceutical compns. for treatment of diseased tissues)

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AN 1999:736476 CAPLUS
DN 131:346535
TI Use of neomycin for treating angiogenesis-related diseases
IN Hu, Guo-Fu; Vallee, Bert L.
PA The Endowment for Research In Human Biology, Inc., USA
SO PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-37
CC 1-8 (Pharmacology)
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PI WO 9958126	A1	19991118	WO 1999-US10269	19990511 <--

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,

ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2331620	AA	19991118	CA 1999-2331620	19990511	<--
AU 9939804	A1	19991129	AU 1999-39804	19990511	<--
EP 1083896	A1	20010321	EP 1999-922915	19990511	

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

US 6482802	B1	20021119	US 2000-700436	20001109
PRAI US 1998-84921P	P	19980511		
WO 1999-US10269	W	19990511		

AB The present invention is directed to using neomycin or an analog thereof as a therapeutic agent to treat angiogenesis-related diseases, which are characterized by excessive, undesired or inappropriate angiogenesis or proliferation of endothelial cells. The present invention is also directed to pharmaceutical compns. comprising: (a) neomycin or an analog and, optionally, (b) another anti-angiogenic agent or an anti-neoplastic agent. The present invention is further directed to a method for screening neomycin analogs having anti-angiogenic activity. A preferred embodiment of the invention relates to using neomycin to treat subjects having such diseases. A dose of 20 ng neomycin/embryo or higher completely inhibited angiogenin-induced angiogenesis in the chorioallantoic membrane (CAM) assay. Neomycin inhibits angiogenin-induced angiogenesis mainly through inhibition of nuclear translocation of angiogenin.

ST neomycin analog angiogenesis inhibition antitumor

IT Eye, disease
(Best's disease; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Intestine, disease
(Crohn's; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Eye, disease
(Eales' disease; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(Ewing's sarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(Kaposi's sarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Bone, disease
(Paget's; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Lymphoproliferative disorders
(Waldenstrom's macroglobulinemia; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Sarcoidosis
(Wegener's; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(Wilms' tumor; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Kidney, neoplasm
(Wilms', inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Nerve, neoplasm
(acoustic neuroma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(acoustic neuroma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(acute lymphocytic leukemia; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(adenocarcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antibiotics
(aminoglycoside; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Artery, disease
(arteritis; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Astrocyte
(astrocytoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(astrocytoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Ulcer
(bacterial and fungal; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Skin, neoplasm
(basal cell carcinoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(basal cell carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(bile duct carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Biliary tract
(bile duct, carcinoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(bladder carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(bronchi carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Bladder
Bladder
Bronchi
Sebaceous gland
Sebaceous gland
(carcinoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Lung, neoplasm
(carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Artery, disease
(carotid, occlusion; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Uterus, neoplasm
(cervix, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(cervix; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Burn
(chem.; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Cartilage
(chondrosarcoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(chondrosarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Notochord
(chordoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(chordoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Chorion
(choriocarcinoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(choriocarcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(colon carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Intestine, neoplasm
(colon, carcinoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Drug delivery systems
(compns. of neomycin and analogs for treatment of angiogenesis-related diseases)

IT Eye, disease
(contact lens overwear; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Transplant rejection
(corneal; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Pituitary gland, anterior lobe
(craniopharyngioma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(craniopharyngioma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Ovary, neoplasm
(cystadenocarcinoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(cystadenocarcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Eye, disease
(diabetic retinopathy; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(embryonal carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Blood vessel
(endothelium; neomycin and analogs as inhibitors of angiogenesis in endothelium and chorioallantoic membrane)

IT Brain, neoplasm
(ependymoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(ependymoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(epithelial carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(fibrosarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Neuroglia
(glioma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(glioma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Immunoglobulins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(heavy chain disease inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(hemangioblastoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Blood vessel, neoplasm
(hemangioma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(hemangioma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Blood vessel, neoplasm
(hemangiosarcoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(hemangiosarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Liver, neoplasm
(hepatoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(hepatoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Capillary vessel
(hereditary hemorrhagic telangiectasia; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Human herpesvirus 3
(herpes zoster from, infections; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Human herpesvirus
Mycobacterium
(infections; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Ovary, neoplasm
Pancreas, neoplasm
Testis, neoplasm
(inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Biological transport
(intracellular; neomycin and analogs are inhibitors of nuclear translocation of angiogenic factors for treatment of angiogenesis-related diseases)

IT Eye, disease
(keratitis; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Eye, disease
(keratoconjunctivitis, epidemic; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(leiomyosarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(leukemia, acute myelocytic; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Antitumor agents
(leukemia, chronic; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)

IT Lipids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(lipid degeneration inhibitors; neomycin, its analogs and other agents

for treatment of angiogenesis-related diseases)
IT Adipose tissue, neoplasm
(liposarcoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(liposarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(lymphangioendotheliosarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Lymphatic system
(lymphangiosarcoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(lymphangiosarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(lymphoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Eye, disease
(macula, degeneration, Stargardt's disease; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Eye, disease
(macula, degeneration; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Brain, neoplasm
Brain, neoplasm
(medulloblastoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(medulloblastoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(melanoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Meninges
Meninges
(meningioma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(meningioma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Mesothelium
(mesothelioma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Erythema
(multiforme; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(multiple myeloma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(myxosarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Angiogenic factors
Hepatocyte growth factor
Interleukin 8
Platelet-derived growth factors
Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(neomycin and analogs are inhibitors of nuclear translocation of angiogenic factors for treatment of angiogenesis-related diseases)
IT Chorioallantois
(neomycin and analogs as inhibitors of angiogenesis in endothelium and chorioallantoic membrane)
IT Angiogenesis inhibitors
Anti-AIDS agents
Antibacterial agents
Antirheumatic agents
Antitumor agents
Antiulcer agents
Antiviral agents
Behcet's syndrome
Cytotoxic agents
Fungicides
Lyme disease
Polycythemia vera
Protein sequences
Protozoacides
Psoriasis
Sarcoidosis
Sickle cell anemia
Sjogren's syndrome
Syphilis
(neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Anthracyclines
Interleukin 12
Interleukin 2
Peptides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Notochord
(neoplasm, chordoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Mammary gland
Prostate gland
Sweat gland
Sweat gland
(neoplasm, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Glaucoma (disease)
(neovascular; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Nerve, neoplasm
Nerve, neoplasm
(neuroblastoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(neuroblastoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Schwann cell
(neurofibroma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(neurofibroma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Artery, disease
Vein
(occlusion; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Neuroglia
(oligodendroglioma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(oligodendroglioma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(osteogenic sarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(ovary; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(pancreas; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(papillary adenocarcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(papillary carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Eye, disease
(pars planitis; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Eye, disease
(periretinal proliferation; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(pinealoma inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Pineal gland
(pinealoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Placental hormones
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(placenta-derived mitogenic factors; neomycin and analogs are inhibitors of nuclear translocation of angiogenic factors for treatment of angiogenesis-related diseases)
IT Eye, disease
(presumed ocular histoplasmosis; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Proliferation inhibition
(proliferation inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Skin, neoplasm
(pseudoxanthoma elasticum; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(pyogenic granuloma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Kidney, neoplasm
(renal cell carcinoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(renal cell carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Eye, disease
(retinitis; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Eye, neoplasm
(retinoblastoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(retinoblastoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Eye, disease
(retinopathy, detachment, chronic; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Eye, disease
(retrolental fibroplasia; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(rhabdomyosarcoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Skin, disease
(rosacea; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Eye, disease
(scleritis; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Drug screening
(screening of neomycin and analogs for treatment of angiogenesis-related diseases)
IT Antitumor agents
(sebaceous gland carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Testis, neoplasm
(seminoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(seminoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Lung, neoplasm
(small-cell carcinoma, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(squamous cell carcinoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(sweat gland; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(synovial membrane tumor inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Lupus erythematosus
(systemic; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(testis; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Toxoplasma gondii
(toxoplasmosis from; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Antitumor agents
(trachoma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Injury
(trauma; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Synovial membrane
(tumors, inhibitors; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Intestine, disease
(ulcerative colitis; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Eye, disease

(uveitis, chronic; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.alpha.-; neomycin and analogs are inhibitors of nuclear translocation of angiogenic factors for treatment of angiogenesis-related diseases)
IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.alpha.; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.-; neomycin and analogs are inhibitors of nuclear translocation of angiogenic factors for treatment of angiogenesis-related diseases)
IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta.; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.gamma.; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT 11103-57-4, Vitamin A
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(deficiency; neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
IT 9001-86-9, Phospholipase C
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; neomycin and analogs as inhibitors of phospholipase C for treatment of angiogenesis-related diseases)
IT 61912-98-9, Insulin-like growth factor 62229-50-9, Epidermal growth factor 65154-06-5, Platelet activating factor 97950-81-7, Angiogenin (human) 106096-92-8, Acidic fibroblast growth factor 106096-93-9, Basic fibroblast growth factor 127464-60-2, Vascular endothelial growth factor 143011-72-7, Granulocyte colony-stimulating factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(neomycin and analogs are inhibitors of nuclear translocation of angiogenic factors for treatment of angiogenesis-related diseases)
IT 66-86-4, Neomycin C 119-04-0, Neomycin B 1404-04-2, Neomycin 2037-48-1, 2-Deoxystreptamine 3947-65-7, Neomycin A 7542-37-2, Paromomycin 11111-23-2, Lividomycin 25546-65-0, Ribostamycin 34051-04-2, Nebramine 35025-95-7, Gentamine C1a 50474-67-4, Xylostasin 51053-37-3, Gentamine C1 51053-38-4, Gentamine C2 84420-34-8, Paromomycin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neomycin and analogs for treatment of angiogenesis-related diseases)
IT 50-18-0, Cyclophosphamide50-35-1, Thalidomide 50-44-2, 6-Mercaptopurine 50-76-0, Dactinomycin 50-91-9, Floxuridine 51-18-3, Triethylenemelamine 51-21-8, Fluorouracil 51-75-2, Mechlorethamine 51-79-6, Urethane 52-24-4, Triethylenethiophosphoramide 52-67-5, D-Penicillamine 53-19-0, Mitotane 53-79-2, Puromycin 54-25-1, 6-Azauridine 54-91-1, Pipobroman 55-98-1, Busulfan 57-22-7, Vincristine 58-05-9, Folinic acid 58-19-5, Dromostanolone 59-05-2, Methotrexate 66-75-1, Uracil mustard 68-76-8, Triaziquone 69-33-0, Tubercidin 84-16-2, Hexestrol 89-38-3, Pteropterin 115-02-6, Azaserine 125-84-8, Aminoglutethimide 127-07-1, Hydroxyurea 147-94-4, Cytarabine 148-82-3, Melphalan 151-56-4D, Aziridine, derive., biological studies 154-42-7, Thioguanine 154-93-8, Carmustine 157-03-9, 6-Diazo-5-oxo-L-norleucine 302-22-7, Chlormadinone acetate 302-49-8, Uredepa 302-70-5, Mechlorethamine oxide hydrochloride 305-03-3, Chlorambucil 320-67-2, Azacitidine 362-07-2, 2-Methoxyestradiol 459-86-9, Mitoguazone 477-30-5, Demecolcine 488-41-5, Mitobronitol 494-03-1, Chlornaphazine 520-85-4, Medroxyprogesterone 522-40-7, Fosfestrol 545-55-1, Triethylenephosphoramide 555-77-1, 2,2',2''-Trichlorotriethylamine 566-48-3, Formestane 576-68-1, Mannomustine 595-33-5, Megestrol acetate 642-83-1, Aceglatone 645-05-6, Altretamine 801-52-5, Porfiromycin 865-21-4, Vinblastine 968-93-4, Testolactone 1402-44-4, Actinomycin F1 1403-28-7, Carzinophilin 1404-00-8, Mitomycin 1404-15-5, Nogalamycin 1508-45-8, Podophyllinic acid 2-ethyl hydrazide 1661-29-6, Meturedepa 1936-40-9, Novembichin 1954-28-5, Etoglucid 1980-45-6, Benzodepa 2363-58-8, Epitiostanol 2608-24-4, Piposulfan 2998-57-4, Estramustine 3094-09-5, Doxifluridine 3546-10-9, Phenesterine 3733-81-1, Defosfamide 3778-73-2, Ifosfamide 3819-34-9, Phenamet 3930-19-6, Streptonigrin 4291-63-8, Cladribine 4342-03-4, Dacarbazine 4533-39-5, Nitracrine 4803-27-4, Anthramycin 5581-52-2, Thiamiprine 5633-18-1, Melengestrol 8052-16-2, Cactinomycin 9014-92-2, Zinostatin 9015-68-3, L-Asparaginase 9042-14-2, Dextran sulfate 10318-26-0, Mitolactol 10540-29-1, Tamoxifen 11006-70-5, Olivomycin 11056-06-7, Bleomycin 13010-47-4, Lomustine 13311-84-7, Flutamide 13425-98-4, Improsulfan 13494-90-1, Gallium nitrate 13647-35-3, Trilostane 13665-88-8, Mopidamol 15663-27-1, Cisplatin 17021-26-0, Calusterone 17902-23-7, Tegafur 18378-89-7, Plicamycin 18883-66-4, Streptozocin 20830-81-3, Daunorubicin 21362-69-6, Mepitiostane 21416-67-1, Razoxane 21679-14-1, Fludarabine 22006-84-4, Denopterin 22089-22-1, Trofosfamide 23110-15-8, Fumagillin 23214-92-8, Doxorubicin 24279-91-2, Carboquone 24280-93-1, Mycophenolic acid 28014-46-2, Polyestradiol phosphate 29069-24-7, Prednimustine 29767-20-2, Teniposide 31698-14-3, Ancitabine 33069-62-4, Paclitaxel 33419-42-0, Etoposide 37270-94-3, Platelet factor 4 37339-90-5, Lentinan 41575-94-4, Carboplatin 41992-23-8, Spirogermanium 42471-28-3, Nimustine 50264-69-2, Lonidamine 50935-04-1, Carubicin 51264-14-3, Amsacrine 52128-35-5, Trimetrexate 53123-88-9, Rapamycin 53643-48-4, Vindesine 53714-56-0, Leuprolide 53910-25-1, Pentostatin 54083-22-6, Zorubicin 54749-90-5, Chlorozotocin 55726-47-1, Enocitabine 56420-45-2, Epirubicin 57773-63-4, Triptorelin 57982-77-1, Buserelin 57998-68-2, Diaziquone 58066-85-6, Miltefosine 58337-35-2, Elliptinium acetate 58957-92-9, Idarubicin 58970-76-6, Ubenimex 58994-96-0, Ranimustine 61163-28-8, .beta.-1,3-Glucan sulfate 61422-45-5, Carmofur 61825-94-3, Oxaliplatin 62435-42-1, Perfosfamide 63612-50-0, Nilutamide 64431-69-2, Aclacinomycin S 65271-80-9, Mitoxanthrone 65646-68-6, Fenretinide 65807-02-5, Goserelin 68247-85-8, Peplomycin 70052-12-9, Eflornithine 70563-58-5, Herbimycin A 71628-96-1, Menogaril 72496-41-4, Pirarubicin 72732-56-0, Piritrexim 74913-06-7, Chromomycin 78186-34-2, Bisantrene 80576-83-6, Edatrexate 82413-20-5, Droloxifene 84088-42-6, Roquinimex 85622-93-1, Temozolomide 86090-08-6, Angiostatin 87806-31-3, Porfimer sodium 89149-10-0, 15-Deoxyspergualin 89778-26-7, Toremifene 90357-06-5, Bicalutamide 92118-27-9, Fotemustine 95058-81-4, Gemcitabine 98631-95-9, Sobuzoxane 99519-84-3, CAI 100286-90-6 102676-47-1, Fadrozole 103775-75-3, Miboplatin 110690-43-2, Emitefur 112809-51-5, Letrozole 112887-68-0, Tomudex 114977-28-5, Docetaxel 120511-73-1, Anastrozole 123948-87-8, Topotecan 126509-46-4, Eponemycin 126595-07-1, Propagermanium 129298-91-5, AGM 1470 130370-60-4, Batimastat 142298-75-7, Ribonuclease inhibitor 154039-60-8, Marimastat 187888-07-9, Endostatin 188417-67-6, CM 101 196858-78-3 197850-48-9 197850-49-0 250331-65-8 250593-25-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(neomycin, its analogs and other agents for treatment of angiogenesis-related diseases)
RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Waksman; US 2799620 A 1957 CAPLUS

L8 ANSWER 17 OF 40 DRUGU COPYRIGHT 2003 THOMSON DERWENT
AN 2001-15379 DRUGU T S
TI Three-arm Phase II study of temozolomide (TMZ) in metastatic melanoma (MM): preliminary results.
AU Arance A; Middleton M; Lorigan P C; Thatcher N
LO Manchester; Sheffield, U.K.
SO ; Proc.Am.Soc.Clin.Oncol. (19, 36 Meet., 573a, 2000)
CODEN: ; 7790
AV Christie Hospital, Manchester, England.
LA English
DT Journal
AB Preliminary results of a randomized Phase II study of p.o. temozolomide alone or combined with s.c. IFN or p.o. thalidomide in 50 patients with metastatic melanoma are reported. Treatment was active and well tolerated in all 3 arms; the most common side-effect was myelosuppression. (conference abstract:-36th Annual Meeting of the American Society of Clinical Oncology, New Orleans, Louisiana, USA, 2000).
SH T Therapeutics
S Adverse Effects
CC 35 Adverse Reactions
50 Biological Response Modifiers
51 Chemotherapy - clinical
CT 64 Clinical Trials
MELANOMA *TR; METASTATIC *TR; THROMBOCYTOPENIA *AE; LEUKOPENIA *AE; DIARRHEA *AE; NEOPLASM *TR; MARROW-DISEASE *AE; GASTROENTEROPATHY *AE; CASES *FT; IN-VIVO *FT; PHASE-II *FT; RANDOM *FT; CYTOSTATIC-COMB. *FT; ADULT *FT; GERIATRICS *FT; CLIN.TRIAL *FT; COMB. *FT
[01] TEMOZOLOMIDE *TR; TEMOZOLOMIDE *AE; CCRG81045 *RN; CYTOSTATIC *FT; P.O. *FT; CYTOSTATICS *FT; TR *FT; AE *FT
RN: 85622-93-1
[02] THALIDOMIDE *TR; THALIDOMIDE *AE; THALIDOMI *RN; CYTOSTATIC *FT; P.O. *FT; SEDATIVES *FT; ANTISEPTICS *FT; TR *FT; AE *FT
RN: 50-35-1
[03] INTERFERON *TR; INTERFERON *AE; INTERFERO *RN; S.C. *FT; INJECTION *FT; VIRUCIDES *FT; CYTOSTATICS *FT; IMMUNOSTIMULANTS *FT; TR *FT; AE *FT
RN: 9008-11-1
FA AB; LA; CT
FS Literature

L8 ANSWER 18 OF 40 DRUGU COPYRIGHT 2003 THOMSON DERWENT
AN 2000-45255 DRUGU T
TI Thalidomide in the treatment of high grade gliomas.
AU Cohen M H
CS FDA
LO Rockville, Md., USA
SO J.Clin.Oncol. (18, No. 19, 3453, 2000) 5 Ref.
CODEN: JCONDN ISSN: 0732-183X
AV United States Food and Drug Administration, Rockville, MD, U.S.A.
LA English
DT Journal
AB A letter discusses a recent phase II trial of thalidomide (TH) in the treatment of recurrent high grade gliomas, in which the response was favorable. A recent phase II trial of temozolomide (TE, Temodar, Schering-Plough) in relapsed anaplastic astrocytoma (AA) patients suggested a response superior to TH. The modest TH efficacy in recurrent disease seems too little to warrant a recommendation of addition to first line therapy. Additional studies with drugs additive or synergistic with TH might be useful.
SH T Therapeutics
CC 51 Chemotherapy - clinical
CT GLIOBLASTOMA *TR; MULTIFORME *TR; ANAPLASTIC *TR; ASTROCYTOMA *TR; GLIOMA *TR; NEOPLASM *TR; IN-VIVO *FT; CASES *FT; CYTOSTATIC *FT
[01] THALIDOMIDE *TR; THALIDOMI *RN; SEDATIVES *FT; ANTISEPTICS *FT; TR *FT
RN: 50-35-1
[02] TEMOZOLOMIDE *TR; TEMODAR *TR; SCHERING-PLOUGH *FT; CCRG81045 *RN; CYTOSTATICS *FT; TR *FT
RN: 85622-93-1
FA AB; LA; CT
FS Literature

L8 ANSWER 19 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2001035295 EMBASE
TI A comparison of treatment results for recurrent malignant gliomas.
AU Nieder C.; Grosu A.L.; Molls M.
CS C. Nieder, Department of Radiation Oncology, Klinikum rechts der Isar, TU Munich, Ismaninger Str. 22, 81675 Munich, Germany
SO Cancer Treatment Reviews, (2000) 26/6 (397-409).
Refs: 62
ISSN: 0305-7372 CODEN: CTREDJ
CY United Kingdom
DT Journal; General Review
FS 016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Retreatment of malignant gliomas may be performed with palliative intent after careful consideration of the risks and benefits, and with special regards to iatrogenic neurotoxicity and quality of life (QOL). This review compares studies of several retreatment strategies (published between 1987 and 2000) based on the quality of their evidence. Depending on both established prognostic factors and previous treatment, individually tailored retreatment strategies are possible. In all studies that included a multivariate analysis of prognostic factors, performance status was the most important. So far, predictive factors for response, which might facilitate patient selection, have not been unequivocally defined. In terms of QOL, single-agent chemotherapy (temozolomide, nitrosoureas, platinum and taxane derivatives) may offer a better therapeutic ratio than polychemotherapy. For glioblastoma multiforme, progression-free survival and QOL were more favourable after temozolomide than procarbazine (level I evidence). The survival of patients after various radiotherapy techniques is broadly similar. However, considerable toxicity is associated with radiosurgery or brachytherapy. Fractionated stereotactic radiotherapy plus radio-sensitizing cytostatic agents has shown promising initial results in small groups of selected patients and awaits further evaluation. Level 2 evidence derived from non-randomized studies does not suggest a substantial prolongation of survival by re-resection as compared with chemotherapy or radiotherapy alone. Level I evidence derived from a randomized trial suggests that application of BCNU polymers significantly improves the outcome after re-resection. However, most studies reported median survival in the range of only 25-35 weeks, thereby emphasizing the need for the development and clinical evaluation of new innovative treatment approaches. .COPYRGT. 2000 Harcourt Publishers Ltd.
CT Medical Descriptors:
*glioblastoma: DT, drug therapy
*glioblastoma: RT, radiotherapy
*glioblastoma: SU, surgery
*glioblastoma: TH, therapy
cancer grading
recurrent cancer: DT, drug therapy

recurrent cancer: RT, radiotherapy
recurrent cancer: SU, surgery
recurrent cancer: TH, therapy
cancer palliative therapy
neurotoxicity: CO, complication
quality of life
prognosis
evidence based medicine
patient selection
cancer chemotherapy
monotherapy
cancer survival
brachytherapy
radiosurgery
stereotaxic surgery
gene therapy
constipation: SI, side effect
somnolence: SI, side effect
comparative study
human
clinical trial
randomized controlled trial
controlled study
review
Drug Descriptors:
temozolomide: CT, clinical trial
temozolomide: CM, drug comparison
temozolomide: DT, drug therapy
nitrosourea derivative: CT, clinical trial
nitrosourea derivative: CB, drug combination
nitrosourea derivative: DT, drug therapy
platinum derivative: CT, clinical trial
platinum derivative: DT, drug therapy
taxane derivative: CT, clinical trial
taxane derivative: DT, drug therapy
procarbazine: CT, clinical trial
procarbazine: CM, drug comparison
procarbazine: DT, drug therapy
radiosensitizing agent: CT, clinical trial
radiosensitizing agent: DT, drug therapy
cytostatic agent: CT, clinical trial
cytostatic agent: DT, drug therapy
carmustine: CT, clinical trial
carmustine: CB, drug combination
carmustine: DT, drug therapy
carboplatin: CT, clinical trial
carboplatin: CB, drug combination
carboplatin: DT, drug therapy
etoposide: CT, clinical trial
etoposide: CB, drug combination
etoposide: DT, drug therapy
ifosfamide: CT, clinical trial
ifosfamide: CB, drug combination
ifosfamide: DT, drug therapy
lomustine: CT, clinical trial
lomustine: CB, drug combination
lomustine: DT, drug therapy
benznidazole: CT, clinical trial
benznidazole: CB, drug combination
benznidazole: DT, drug therapy
alpha interferon: CT, clinical trial
alpha interferon: CB, drug combination
alpha interferon: DT, drug therapy
tamoxifen: CT, clinical trial
tamoxifen: CB, drug combination
tamoxifen: DT, drug therapy
anthracycline antibiotic agent: CT, clinical trial
anthracycline antibiotic agent: DT, drug therapy
taxol: CT, clinical trial
taxol: DT, drug therapy
irinotecan: CT, clinical trial
irinotecan: DT, drug therapy
retinoic acid: CT, clinical trial
retinoic acid: DT, drug therapy
cisplatin: CT, clinical trial
cisplatin: DT, drug therapy
thalidomide: AE, adverse drug reaction
thalidomide: CT, clinical trial
thalidomide: DO, drug dose
thalidomide: DT, drug therapy
RN (temozolomide) 85622-93-1; (procarbazine) 366-70-1, 671-16-9; (carmustine) 154-93-8; (carboplatin) 41575-94-4; (etoposide) 33419-42-0; (ifosfamide) 3778-73-2; (lomustine) 13010-47-4; (benznidazole) 22994-85-0; (tamoxifen) 10540-29-1; (taxol) 33069-62-4; (irinotecan) 100286-90-6; (retinoic acid) 302-79-4; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (thalidomide) 50-35-1

L8 ANSWER 20 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2000429822 EMBASE
TI Novel chemotherapeutic agents for the treatment of brain cancer.
AU Newton H.B.
CS H.B. Newton, Department of Neurology, The Ohio State University Hospitals, 465 Means Hall, 1654 Upham Drive, Columbus, OH 43210, United States. newton.12@osu.edu
SO Expert Opinion on Investigational Drugs, (2000) 9/12 (2815-2829). Refs: 97
ISSN: 1354-3784 CODEN: EOIDER
CY United Kingdom
DT Journal; General Review
FS 008 Neurology and Neurosurgery
016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Brain cancer encompasses both primary and metastatic brain tumours and accounts for over 120,000 new patients each year. Despite aggressive therapy, the majority of patients with brain cancer have poor prognosis and have brief survival intervals. Current chemotherapy drugs, used alone or in combination, have minimal or only modest activity. Novel agents that have recently been applied to brain cancer include temozolomide, irinotecan and paclitaxel. Temozolomide is a DNA alkylating agent, irinotecan inhibits DNA topoisomerase I and paclitaxel binds to microtubules and induces polymerisation. Neoplastic angiogenesis and brain tumour invasion are also targets for therapeutic intervention with new agents such as thalidomide, suramin and marimastat. All of these agents have demonstrated activity against brain cancer in vitro. Several of the drugs, in particular temozolomide, paclitaxel and irinotecan, have entered preliminary clinical trials and have demonstrated some efficacy. However, chemotherapy for primary brain tumours remains rather non-specific and mostly ineffective. The use of chemotherapy may be more effective against selected metastatic brain tumours. Continued basic research is needed to further elucidate the genetic basis of transformation, tumour invasion and angiogenesis. It is hoped that this research will lead to new therapeutic targets for drug design and development. In addition, new strategies must be developed to overcome the problem of chemotherapy resistance.
CT Medical Descriptors:
*brain cancer: DT, drug therapy
drug mechanism
DNA alkylation
enzyme inhibition
microtubule assembly
drug binding
angiogenesis
tumor vascularization
cancer invasion
drug targeting
in vitro study
antineoplastic activity
drug efficacy
brain metastasis: DT, drug therapy
drug structure
drug bioavailability
glioblastoma: DT, drug therapy
glioma: DT, drug therapy
pain: SI, side effect
muscle stiffness: SI, side effect
side effect: SI, side effect
human
nonhuman
mouse
clinical trial
phase 1 clinical trial
phase 2 clinical trial
phase 3 clinical trial
animal experiment
animal model
controlled study
review
Drug Descriptors:
*antineoplastic agent: AE, adverse drug reaction
*antineoplastic agent: CT, clinical trial
*antineoplastic agent: AN, drug analysis
*antineoplastic agent: CB, drug combination
*antineoplastic agent: DO, drug dose
*antineoplastic agent: DT, drug therapy
*antineoplastic agent: PK, pharmacokinetics
*antineoplastic agent: PD, pharmacology
temozolomide: CT, clinical trial
temozolomide: AN, drug analysis
temozolomide: DO, drug dose
temozolomide: DT, drug therapy
temozolomide: PK, pharmacokinetics
temozolomide: PD, pharmacology
irinotecan: CT, clinical trial
irinotecan: AN, drug analysis
irinotecan: CB, drug combination
irinotecan: DO, drug dose
irinotecan: DT, drug therapy
irinotecan: PK, pharmacokinetics
irinotecan: PD, pharmacology
taxol: CT, clinical trial
taxol: AN, drug analysis
taxol: DO, drug dose
taxol: DT, drug therapy
taxol: PK, pharmacokinetics
taxol: PD, pharmacology
alkylating agent: CT, clinical trial
alkylating agent: AN, drug analysis
alkylating agent: DO, drug dose
alkylating agent: DT, drug therapy
alkylating agent: PK, pharmacokinetics
alkylating agent: PD, pharmacology
DNA topoisomerase: EC, endogenous compound
DNA topoisomerase inhibitor: CT, clinical trial
DNA topoisomerase inhibitor: AN, drug analysis
DNA topoisomerase inhibitor: CB, drug combination
DNA topoisomerase inhibitor: DO, drug dose
DNA topoisomerase inhibitor: DT, drug therapy
DNA topoisomerase inhibitor: PK, pharmacokinetics
DNA topoisomerase inhibitor: PD, pharmacology
thalidomide: CT, clinical trial
thalidomide: AN, drug analysis
thalidomide: CB, drug combination
thalidomide: DO, drug dose
thalidomide: DT, drug therapy
thalidomide: PD, pharmacology
suramin: PD, pharmacology
marimastat: AE, adverse drug reaction
marimastat: CT, clinical trial
marimastat: CB, drug combination
marimastat: CR, drug concentration
marimastat: DO, drug dose
marimastat: DT, drug therapy
marimastat: PK, pharmacokinetics
marimastat: PD, pharmacology
procarbazine: DT, drug therapy
carmustine: CT, clinical trial
carmustine: CB, drug combination
carmustine: DT, drug therapy
cisplatin: CB, drug combination
topotecan: CB, drug combination
isotretinoin: CB, drug combination
alpha interferon: CB, drug combination
angiogenesis inhibitor: AN, drug analysis
angiogenesis inhibitor: PD, pharmacology
angiostatin: AN, drug analysis
angiostatin: PD, pharmacology
endostatin: AN, drug analysis
endostatin: PD, pharmacology
fumagillol chloroacetylcarbamate: AN, drug analysis
fumagillol chloroacetylcarbamate: PD, pharmacology
su 6668: AN, drug analysis
su 6668: PD, pharmacology
platelet derived growth factor: EC, endogenous compound
basic fibroblast growth factor: EC, endogenous compound
carboplatin: CB, drug combination
carboplatin: DT, drug therapy
etoposide: CB, drug combination
etoposide: DO, drug dose
etoposide: DT, drug therapy
protein p53: EC, endogenous compound
lomustine: DT, drug therapy
vincristine: DT, drug therapy
cytochrome P450: EC, endogenous compound
unindexed drug
unclassified drug
temodar
RN (temozolomide) 85622-93-1; (irinotecan) 100286-90-6; (taxol) 33069-62-4; (DNA topoisomerase) 80449-01-0; (thalidomide) 50-35-1; (suramin) 129-46-4, 145-63-1; (marimastat) 154039-60-8; (procarbazine) 366-70-1, 671-16-9; (carmustine) 154-93-8; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (topotecan) 119413-54-6, 123948-87-8; (isotretinoin) 4759-48-2; (angiostatin) 172642-30-7, 86090-08-6; (endostatin) 187888-07-9; (fumagillol chloroacetylcarbamate) 129298-91-5;

(basic fibroblast growth factor) 106096-93-9; (carboplatin) 41575-94-4; (etoposide) 33419-42-0; (lomustine) 13010-47-4; (vincristine) 57-22-7; (cytochrome P450) 9035-51-2
CN Temodar; Camptosar; Cpt 11; Tnp 470; Su 6668; Taxol

L8 ANSWER 21 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2000426761 EMBASE
TI Chemotherapy in malignant gliomas.
AU Burton G.V.
CS Dr. G.V. Burton, Feist-Weiller Cancer Center, LA State Univ. Health Science Center, 1501 Kings HW, Shreveport, LA 71130-3932, United States
SO Seminars in Neurosurgery, (2000) 11/3 (373-385).
Refs: 92
ISSN: 1526-8012 CODEN: SNEEAH
CY United States
DT Journal; General Review
FS 008 Neurology and Neurosurgery
016 Cancer
037 Drug Literature Index
LA English
SL English
AB Current chemotherapy approaches to patients with malignant gliomas have little impact on patient outcomes. Surgical and radiotherapy, although providing the majority of benefit, have little potential for significant further improvement of patient survival. Medical therapy, especially with expanding knowledge relative to tumor resistance, oncogenesis pathways, and angiogenesis, has great potential for altering the outcomes of patients with malignant gliomas. New cytotoxic agents such as temozolomide and CPT-11 appear to have significant activity; however, anti-angiogenesis therapy, gene therapies directed at oncogenic pathways, and immuno-toxin constructs may have the greatest potential. Only by participation in clinical trials can these new agents be developed to benefit future patients with malignant gliomas.
CT Medical Descriptors:
*glioblastoma: DT, drug therapy
*glioblastoma: RT, radiotherapy
*glioblastoma: SU, surgery
treatment outcome
cancer survival
cancer resistance
carcinogenesis
angiogenesis
prognosis
drug effect
gene therapy
drug efficacy
drug cytotoxicity
drug activity
cancer immunotherapy
adoptive immunotherapy
multimodality cancer therapy
cancer adjuvant therapy
human
review
Drug Descriptors:
*antineoplastic agent: CB, drug combination
*antineoplastic agent: DT, drug therapy
*antineoplastic agent: IA, intraarterial drug administration
*antineoplastic agent: TU, intratumoral drug administration
*antineoplastic agent: IV, intravenous drug administration
*angiogenesis inhibitor: DT, drug therapy
*thalidomide: DT, drug therapy
*nalpha [2 [arginylprolyl(4 hydroxyprolyl)glycyl[3 (2 thienyl)alanyl]serylprolylamino] 3 (4 methoxyphenyl)propyl]arginine: DT, drug therapy
*BCG vaccine: DT, drug therapy
*picibanil: DT, drug therapy
*levamisole: DT, drug therapy
*interferon: DT, drug therapy
*immunotoxin: DT, drug therapy
*immunotoxin: TU, intratumoral drug administration
*polymer: CB, drug combination
*polymer: DT, drug therapy
lomustine: CB, drug combination
lomustine: DT, drug therapy
carmustine: CB, drug combination
carmustine: DT, drug therapy
carmustine: IA, intraarterial drug administration
carmustine: TU, intratumoral drug administration
carmustine: IV, intravenous drug administration
semustine: CB, drug combination
semustine: DT, drug therapy
teniposide: CB, drug combination
teniposide: DT, drug therapy
meprednisone: CB, drug combination
meprednisone: DT, drug therapy
procarbazine: CB, drug combination
procarbazine: DT, drug therapy
mitolactol: CB, drug combination
mitolactol: DT, drug therapy
dacarbazine: CB, drug combination
dacarbazine: DT, drug therapy
streptozocin: DT, drug therapy
misonidazole: CB, drug combination
misonidazole: DT, drug therapy
hydroxyurea: CB, drug combination
hydroxyurea: DT, drug therapy
fluorouracil: CB, drug combination
fluorouracil: DT, drug therapy
diaziquone: CB, drug combination
diaziquone: DT, drug therapy
1 (2 chloroethyl) 3 (2,6 dioxo 3 piperidyl) 1 nitrosourea: DT, drug therapy
mitomycin C: CB, drug combination
mitomycin C: DT, drug therapy
mercaptopurine: CB, drug combination
mercaptopurine: DT, drug therapy
broxuridine: DT, drug therapy
temozolomide: DT, drug therapy
irinotecan: DT, drug therapy
unindexed drug
RN (thalidomide) 50-35-1; (nalpha [2 [arginylprolyl(4 hydroxyprolyl)glycyl[3 (2 thienyl)alanyl]serylprolylamino] 3 (4 methoxyphenyl)propyl]arginine) 159768-75-9; (picibanil) 39325-01-4; (levamisole) 14769-73-4, 16595-80-5; (lomustine) 13010-47-4; (carmustine) 154-93-8; (semustine) 13909-09-6; (teniposide) 29767-20-2; (meprednisone) 1247-42-3; (procarbazine) 366-70-1, 671-16-9; (mitolactol) 10318-26-0; (dacarbazine) 4342-03-4; (streptozocin) 18883-66-4; (misonidazole) 13551-87-6; (hydroxyurea) 127-07-1; (fluorouracil) 51-21-8; (diaziquone) 57998-68-2; (1 (2 chloroethyl) 3 (2,6 dioxo 3 piperidyl) 1 nitrosourea) 13909-02-9; (mitomycin C) 50-07-7, 74349-48-7; (mercaptopurine) 31441-78-8, 50-44-2, 6112-76-1; (broxuridine) 59-14-3; (temozolomide) 85622-93-1; (irinotecan) 100286-90-6

L8 ANSWER 22 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2000393804 EMBASE
TI Thalidomide in the treatment of high-grade gliomas [4].
AU Cohen M.H.
CS M.H. Cohen, United States Food/Drug Admin., Rockville, MD, United States
SO Journal of Clinical Oncology, (1 Oct 2000) 18/19 (3453).
Refs: 5
ISSN: 0732-183X CODEN: JCONDN
CY United States
DT Journal; Letter
FS 008 Neurology and Neurosurgery
016 Cancer
037 Drug Literature Index
LA English
CT Medical Descriptors:
*glioblastoma
*glioma
tumor recurrence
prognosis
drug efficacy
drug potentiation
human
major clinical study
clinical trial
phase 2 clinical trial
adult
letter
priority journal
Drug Descriptors:
*thalidomide: CT, clinical trial
*thalidomide: PD, pharmacology
temozolomide: CT, clinical trial
temozolomide: PD, pharmacology
procarbazine: CT, clinical trial
procarbazine: PD, pharmacology
carmustine: CT, clinical trial
carmustine: PD, pharmacology
polyanhydride
temodar
RN (thalidomide) 50-35-1; (temozolomide) 85622-93-1; (procarbazine) 366-70-1, 671-16-9; (carmustine) 154-93-8
CN (1) Temodar; Gliadel
CO (1) Schering Plough (United States)

L8 ANSWER 23 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2000358231 EMBASE
TI Chemotherapy: Low-grade gliomas of the hypothalamus and thalamus.
AU Packer R.J.
CS Dr. R.J. Packer, Children's National Medical Center, 111 Michigan Avenue, NW, Washington, DC 20010, United States. rpacker@cnmc.org
SO Pediatric Neurosurgery, (2000) 32/5 (259-263).
Refs: 20
ISSN: 1016-2291 CODEN: PDNEEV
CY Switzerland
DT Journal; Article
FS 007 Pediatrics and Pediatric Surgery
008 Neurology and Neurosurgery
037 Drug Literature Index
LA English
SL English
AB Chemotherapy is an increasing component of the management of diencephalic gliomas. It can result in tumor shrinkage and significant disease control in some patients. However, decisions concerning the institution of treatment should be based on the goals of treatment. Factors include: (1) age of the patient; (2) whether the child has neurofibromatosis type 1; (3) tumor size and location; (4) the potential sequelae of radiotherapy, and (5) the acute and long-term toxicity of the chemotherapeutic approach utilized. The erratic natural history of diencephalic tumors confounds evaluation of efficacy of the regimen chosen. Copyright (C) 2000 S. Karger AG, Basel.
CT Medical Descriptors:
*cancer chemotherapy
*glioma: DT, drug therapy
cancer grading
hypothalamus tumor
thalamus
diencephalon
tumor volume
cancer control
medical decision making
age
tumor localization
neurofibromatosis
cancer radiotherapy
acute toxicity
chronic toxicity
risk benefit analysis
human
article
priority journal
Drug Descriptors:
vincristine: CB, drug combination
vincristine: DO, drug dose
vincristine: DT, drug therapy
vincristine: IV, intravenous drug administration
carboplatin: CB, drug combination
carboplatin: DT, drug therapy
cyclophosphamide: DT, drug therapy
etoposide: CB, drug combination
etoposide: DT, drug therapy
etoposide: IV, intravenous drug administration
etoposide: PO, oral drug administration
dactinomycin: CB, drug combination
dactinomycin: DT, drug therapy
cisplatin: CB, drug combination
cisplatin: DT, drug therapy
chlormethine: CB, drug combination
chlormethine: DT, drug therapy
prednisone: CB, drug combination
prednisone: DT, drug therapy
procarbazine: CB, drug combination
procarbazine: DT, drug therapy
thioguanine derivative: CB, drug combination
thioguanine derivative: DT, drug therapy
mitolactol: CB, drug combination
mitolactol: DT, drug therapy
lomustine: CB, drug combination
lomustine: DT, drug therapy
temozolomide
thalidomide
RN (vincristine) 57-22-7; (carboplatin) 41575-94-4; (cyclophosphamide) 50-18-0; (etoposide) 33419-42-0; (dactinomycin) 1402-38-6, 1402-58-0, 50-76-0; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (chlormethine) 51-75-2, 55-86-7, 82905-71-3; (prednisone) 53-03-2; (procarbazine) 366-70-1, 671-16-9; (mitolactol) 10318-26-0; (lomustine) 13010-47-4; (temozolomide) 85622-93-1; (thalidomide) 50-35-1
CN CCNU

L8 ANSWER 24 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2000351127 EMBASE
TI Drugs of choice for cancer chemotherapy.
SO Medical Letter on Drugs and Therapeutics, (18 Sep 2000) 42/1087-1088

(83-92).
ISSN: 0025-732X CODEN: MELEAP
CY United States
DT Journal; General Review
FS 016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
CT Medical Descriptors:
*cancer chemotherapy
*cancer: DT, drug therapy
*cancer: RT, radiotherapy
*cancer: SU, surgery
drug choice
drug indication
United States
Canada
food and drug administration
cancer surgery
cancer radiotherapy
acute toxicity
chronic toxicity
cancer combination chemotherapy
bone marrow depression: SI, side effect
mouth ulcer: SI, side effect
digestive system ulcer: SI, side effect
kidney injury: SI, side effect
hypophosphatemia: SI, side effect
human
review
Drug Descriptors:
*antineoplastic agent: AE, adverse drug reaction
*antineoplastic agent: CB, drug combination
*antineoplastic agent: DT, drug therapy
*antineoplastic agent: TO, drug toxicity
cisplatin: AE, adverse drug reaction
cisplatin: CB, drug combination
cisplatin: DT, drug therapy
cisplatin: TO, drug toxicity
etoposide: AE, adverse drug reaction
etoposide: CB, drug combination
etoposide: DT, drug therapy
etoposide: TO, drug toxicity
mithramycin: AE, adverse drug reaction
mithramycin: DT, drug therapy
mithramycin: TO, drug toxicity
UFT: AE, adverse drug reaction
UFT: DT, drug therapy
UFT: TO, drug toxicity
9 cis retinoic acid: AE, adverse drug reaction
9 cis retinoic acid: DT, drug therapy
9 cis retinoic acid: TO, drug toxicity
altretamine: AE, adverse drug reaction
altretamine: DT, drug therapy
altretamine: TO, drug toxicity
anastrozole: AE, adverse drug reaction
anastrozole: DT, drug therapy
anastrozole: TO, drug toxicity
asparaginase: AE, adverse drug reaction
asparaginase: CB, drug combination
asparaginase: DT, drug therapy
asparaginase: TO, drug toxicity
azacitidine: AE, adverse drug reaction
azacitidine: DT, drug therapy
azacitidine: TO, drug toxicity
4 [1 (5,6,7,8 tetrahydro 3,5,5,8,8 pentamethyl 2 naphthyl)ethenyl]benzoic acid: AE, adverse drug reaction
4 [1 (5,6,7,8 tetrahydro 3,5,5,8,8 pentamethyl 2 naphthyl)ethenyl]benzoic acid: DT, drug therapy
4 [1 (5,6,7,8 tetrahydro 3,5,5,8,8 pentamethyl 2 naphthyl)ethenyl]benzoic acid: TO, drug toxicity
BCG vaccine: AE, adverse drug reaction
BCG vaccine: DT, drug therapy
BCG vaccine: TO, drug toxicity
denileukin diftitox: AE, adverse drug reaction
denileukin diftitox: DT, drug therapy
denileukin diftitox: TO, drug toxicity
epirubicin: AE, adverse drug reaction
epirubicin: CB, drug combination
epirubicin: DT, drug therapy
epirubicin: TO, drug toxicity
gemtuzumab: AE, adverse drug reaction
gemtuzumab: DT, drug therapy
gemtuzumab: TO, drug toxicity
alpha2b interferon: AE, adverse drug reaction
alpha2b interferon: DT, drug therapy
alpha2b interferon: TO, drug toxicity
temozolomide: AE, adverse drug reaction
temozolomide: DT, drug therapy
temozolomide: TO, drug toxicity
thalidomide: AE, adverse drug reaction
thalidomide: DT, drug therapy
thalidomide: TO, drug toxicity
cytarabine: AE, adverse drug reaction
cytarabine: CB, drug combination
cytarabine: DO, drug dose
cytarabine: DT, drug therapy
cytarabine: TO, drug toxicity
cytarabine: TL, intrathecal drug administration
cytarabine: IV, intravenous drug administration
dacarbazine: AE, adverse drug reaction
dacarbazine: CB, drug combination
dacarbazine: DT, drug therapy
dacarbazine: TO, drug toxicity
dactinomycin: AE, adverse drug reaction
dactinomycin: CB, drug combination
dactinomycin: DT, drug therapy
dactinomycin: TO, drug toxicity
daunorubicin: AE, adverse drug reaction
daunorubicin: CB, drug combination
daunorubicin: DT, drug therapy
daunorubicin: TO, drug toxicity
diethylstilbestrol: AE, adverse drug reaction
diethylstilbestrol: DT, drug therapy
diethylstilbestrol: TO, drug toxicity
estramustine phosphate sodium: AE, adverse drug reaction
estramustine phosphate sodium: DT, drug therapy
estramustine phosphate sodium: TO, drug toxicity
floxuridine: AE, adverse drug reaction
floxuridine: DT, drug therapy
floxuridine: TO, drug toxicity
fludarabine phosphate: AE, adverse drug reaction
fludarabine phosphate: CB, drug combination
fludarabine phosphate: DT, drug therapy
fludarabine phosphate: TO, drug toxicity
fluorouracil: AE, adverse drug reaction
fluorouracil: CB, drug combination
fluorouracil: DT, drug therapy
fluorouracil: TO, drug toxicity
fluoxymesterone: AE, adverse drug reaction
fluoxymesterone: DT, drug therapy
fluoxymesterone: TO, drug toxicity
flutamide: AE, adverse drug reaction
flutamide: DT, drug therapy
flutamide: TO, drug toxicity
unindexed drug
unclassified drug
theracys
bicalutamide
bleomycin sulfate
busulfan
capecitabine
carboplatin
carmustine
chlorambucil
2 chlorodeoxyadenosine
cyclophosphamide
fosfestrol
taxotere
doxorubicin
ellence
exemestane
gallium nitrate
gemcitabine
mylotarg
goserelin
hydroxyurea
idarubicin
ifosfamide
recombinant alpha2a interferon
recombinant alpha2b interferon
alphan3 interferon
recombinant interleukin 2
irinotecan
isotretinoin
letrozole
folinate calcium
leuprorelin
lomustine
chlormethine
megestrol acetate
melphalan
mercaptopurine
mesna
methotrexate
mitomycin C
mitotane
mitoxantrone
nilutamide
octreotide
oxaliplatin
taxol
asparaginase macrogol
pentostatin
mithricin
procarbazine
rituximab
streptozocin
tamoxifen citrate
temodar
teniposide
thiotepa
topotecan
toremifene
trastuzumab
retinoic acid
valrubicin
vinblastine sulfate
vincristine sulfate
navelbine
tioguanine
aminoglutethimide
chlorozotocin
medroxyprogesterone acetate
tarabine
etretinate
thalidomid

RN (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (etoposide) 33419-42-0; (mithramycin) 18378-89-7; (UFT) 74578-38-4; (altretamine) 15468-34-5, 2975-00-0, 645-05-6; (anastrozole) 120511-73-1; (asparaginase) 9015-68-3; (azacitidine) 320-67-2, 52934-49-3; (4 [1 (5,6,7,8 tetrahydro 3,5,5,8,8 pentamethyl 2 naphthyl)ethenyl]benzoic acid) 153559-49-0; (epirubicin) 56390-09-1, 56420-45-2; (alpha2b interferon) 99210-65-8; (temozolomide) 85622-93-1; (thalidomide) 50-35-1; (cytarabine) 147-94-4, 69-74-9; (dacarbazine) 4342-03-4; (dactinomycin) 1402-38-6, 1402-58-0, 50-76-0; (daunorubicin) 12707-28-7, 20830-81-3, 23541-50-6; (diethylstilbestrol) 30498-85-2, 56-53-1; (estramustine phosphate sodium) 52205-73-9; (floxuridine) 50-91-9; (fludarabine phosphate) 75607-67-9; (fluorouracil) 51-21-8; (fluoxymesterone) 76-43-7; (flutamide) 13311-84-7; (bicalutamide) 90357-06-5; (bleomycin sulfate) 9041-93-4; (busulfan) 55-98-1; (capecitabine) 154361-50-9; (carboplatin) 41575-94-4; (carmustine) 154-93-8; (chlorambucil) 305-03-3; (2 chlorodeoxyadenosine) 4291-63-8; (cyclophosphamide) 50-18-0; (fosfestrol) 4719-75-9, 522-40-7; (taxotere) 114977-28-5; (doxorubicin) 23214-92-8, 25316-40-9; (exemestane) 107868-30-4; (gallium nitrate) 13494-90-1; (gemcitabine) 103882-84-4; (goserelin) 65807-02-5; (hydroxyurea) 127-07-1; (idarubicin) 57852-57-0, 58957-92-9; (ifosfamide) 3778-73-2; (recombinant alpha2b interferon) 98530-12-2; (recombinant interleukin 2) 110942-02-4; (irinotecan) 100286-90-6; (isotretinoin) 4759-48-2; (letrozole) 112809-51-5; (folinate calcium) 1492-18-8, 51057-63-7; (leuprorelin) 53714-56-0, 74381-53-6; (lomustine) 13010-47-4; (chlormethine) 51-75-2, 55-86-7, 82905-71-3; (megestrol acetate) 595-33-5; (melphalan) 148-82-3; (mercaptopurine) 31441-78-8, 50-44-2, 6112-76-1; (mesna) 19767-45-4, 3375-50-6; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (mitomycin C) 50-07-7, 74349-48-7; (mitotane) 53-19-0; (mitoxantrone) 65271-80-9, 70476-82-3; (nilutamide) 63612-50-0; (octreotide) 83150-76-9; (oxaliplatin) 61825-94-3; (taxol) 33069-62-4; (pentostatin) 53910-25-1; (procarbazine) 366-70-1, 671-16-9; (rituximab) 174722-31-7; (streptozocin) 18883-66-4; (tamoxifen citrate) 54965-24-1; (teniposide) 29767-20-2; (thiotepa) 52-24-4; (topotecan) 119413-54-6, 123948-87-8; (toremifene) 89778-26-7; (trastuzumab) 180288-69-1; (retinoic acid) 302-79-4; (valrubicin) 56124-62-0; (vinblastine sulfate) 143-67-9; (vincristine sulfate) 2068-78-2; (navelbine) 71486-22-1; (tioguanine) 154-42-7; (aminoglutethimide) 125-84-8; (chlorozotocin) 54749-90-5, 58484-07-4; (medroxyprogesterone acetate) 71-58-9; (etretinate) 54350-48-0

CN (1) Panretin; (2) Hexalen; (3) Arimidex; (4) Elspar; (5) Mylosar; (6) Targretin; (7) Theracys; (8) Casodex; (9) Blenoxane; (10) Myleran; (11) Xeloda; (12) Paraplatin; (13) Bicnu; (14) Gliadel; (15) Leukeran; (16) Platinol; (17) Leustatin; (18) Cytoxan; (19) Neosar; (20) Cytosar u; (21) Dtic dome; (22) Cosmegen; (23) Cerubidine; (24) Daunoxome; (25) Ontak; (26) Stilphostrol; (27) Taxotere; (28) Adriamycin; (29) Doxil; (30) Ellence; (31) Emcyt; (32) Vepesid; (33) Aromasin; (34) Fudr; (35) Fludara; (36) Adrucil; (37) Halotestin; (39) Eulexin; (40) Gamite; (41) Gemzar; (42) Mylotarg; (43) Zoladex; (44) Hydrea; (45) Idamycin; (46) Ifex; (47) Roferon a; (49) Intron A; (50) Alferon n; (51) Proleukin; (52) Camptosar; (53) Accutane; (54) Femara; (55) Wellcovorin; (56) Lupron; (57) Lupron

depot; (58) Ceenu; (59) Mustargen; (60) Megace; (61) Alkeran; (62) Purinethol; (63) Mesnex; (64) Folex; (65) Mutamycin; (66) Lysodren; (67) Novantrone; (68) Nilandron; (69) Sandostatin; (70) Eloxatine; (71) Taxol; (72) Oncaspar; (73) Nipent; (74) Mithricin; (75) Matulane; (76) Rituxan; (77) Zanosar; (78) Nolvadex; (79) Temodar; (80) Vumon; (81) Thalomid; (82) Thioplex; (83) Hycamtin; (85) Fareston; (86) Herceptin; (87) Vesanoid; (88) Valstar; (89) Velban; (90) Oncovin; (91) Navelbine; Kidrolase; Pharmorubicin; Buflex; Uromitexan; Natulan; Tamofen; Lanvis; Velbe; Cytadren; Dcnu; Depo provera; Provera; Rubex; Tarabine; Tegison; UFT; Vincasar; Thalidomid

CO (2) United States Bioscience; (7) Connaught; (17) Ortho; (23) Bedford; (24) Gilead; (25) Ligand Pharmaceuticals; (26) Bayer; (29) Alza; (35) Berlex; (40) Solopak; (42) Wyeth Ayerst; (50) Interferon Laboratories; (51) Chiron; (57) TAP; (59) Merck; (68) Hoechst Marion Roussel; (69) Novartis; (70) Sanofi Synthelabo; (72) Rhone Poulenc Rorer; (73) Supergen; (74) Pfizer; (76) Idec; (77) Pharmacia Upjohn; (78) Zeneca; (80) Bristol; (81) Celgene; (82) Immunex; (83) SmithKline Beecham; (84) Schering; (85) Schering Plough; (86) Genentech; (87) Hoffmann La Roche; (88) Medeva; (90) Lilly; (91) Glaxo Wellcome

L8 ANSWER 25 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2000287739 EMBASE
TI [Development of new antineoplastic agents with known and novel mechanisms of action].
ENTWICKLUNG NEUER ANTINEOPLASTISCH WIRKSAMER SUBSTANZEN MIT BEKANNTEN UND NEUEN WIRKUNGSPRINZIPIEN.
AU Lipp H.-P.
CS Dr. H.-P. Lipp, Universitatsapotheke, Rontgenweg 9, 72076 Tubingen, Germany
SO Krankenhauspharmazie, (2000) 21/8 (396-419).
Refs: 136
ISSN: 0173-7597 CODEN: KRANDZ
CY Germany
DT Journal; Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English; German
SL English
AB It is a great challenge to find new cytostatics with well-known mechanisms of action which will have (I) a greater therapeutic index, (II) an improved pharmacokinetic behaviour, (III) additional intracellularly located targets or (IV) increased activity against resistant cells. In this regard, examples like Oxaliplatin, TAS-103, CI-941, the Multitargeted Antifolate (MTA), Temozolomide or Eniluracil represent encouraging developments. In the meantime several inhibitors of farnesyl transferases, matrix metalloproteinases, telomerase or different kinases as well as antisense-oligonucleotides or tirapazamine are matter of clinical research. Additionally, substances like SDZ PSC 833 or Benzylguanine may help to overcome multi-resistant conditions.
CT Medical Descriptors:
*cancer chemotherapy
cancer research
drug research
antineoplastic activity
drug mechanism
drug structure
drug metabolism
cancer: DT, drug therapy
cancer: TH, therapy
drug induced disease: SI, side effect
neurotoxicity: SI, side effect
bone marrow toxicity: SI, side effect
melanoma: DT, drug therapy
human
clinical trial
phase 1 clinical trial
article
Drug Descriptors:
*antineoplastic agent: AE, adverse drug reaction
*antineoplastic agent: CT, clinical trial
*antineoplastic agent: AD, drug administration
*antineoplastic agent: AN, drug analysis
*antineoplastic agent: CB, drug combination
*antineoplastic agent: DV, drug development
*antineoplastic agent: DO, drug dose
*antineoplastic agent: PK, pharmacokinetics
*antineoplastic agent: PD, pharmacology
*antineoplastic agent: PO, oral drug administration
*alkylating agent: AE, adverse drug reaction
*alkylating agent: CT, clinical trial
*alkylating agent: AD, drug administration
*alkylating agent: AN, drug analysis
*alkylating agent: DV, drug development
*alkylating agent: DO, drug dose
*alkylating agent: PK, pharmacokinetics
*alkylating agent: PD, pharmacology
*alkylating agent: PO, oral drug administration
*DNA topoisomerase inhibitor: AN, drug analysis
*DNA topoisomerase inhibitor: DV, drug development
*DNA topoisomerase inhibitor: PK, pharmacokinetics
*DNA topoisomerase inhibitor: PD, pharmacology
*anthracycline antibiotic agent: AN, drug analysis
*anthracycline antibiotic agent: DV, drug development
*anthracycline antibiotic agent: PK, pharmacokinetics
*anthracycline antibiotic agent: PD, pharmacology
*folic acid antagonist: AN, drug analysis
*folic acid antagonist: DV, drug development
*folic acid antagonist: PK, pharmacokinetics
*folic acid antagonist: PD, pharmacology
*antisense oligonucleotide: DV, drug development
antineoplastic antibiotic: AN, drug analysis
antineoplastic antibiotic: DV, drug development
antineoplastic antibiotic: PK, pharmacokinetics
antineoplastic antibiotic: PD, pharmacology
temozolomide: CT, clinical trial
temozolomide: AD, drug administration
temozolomide: AN, drug analysis
temozolomide: DV, drug development
temozolomide: DO, drug dose
temozolomide: DT, drug therapy
temozolomide: PK, pharmacokinetics
temozolomide: PD, pharmacology
temozolomide: PO, oral drug administration
penclomedine: AE, adverse drug reaction
penclomedine: CT, clinical trial
penclomedine: AN, drug analysis
penclomedine: DV, drug development
penclomedine: DO, drug dose
penclomedine: DT, drug therapy
penclomedine: PK, pharmacokinetics
penclomedine: PD, pharmacology
camptothecin derivative: CT, clinical trial
camptothecin derivative: AD, drug administration
camptothecin derivative: AN, drug analysis
camptothecin derivative: DV, drug development
camptothecin derivative: DO, drug dose
camptothecin derivative: DT, drug therapy
camptothecin derivative: PK, pharmacokinetics
camptothecin derivative: PD, pharmacology
camptothecin derivative: PO, oral drug administration
9 aminocamptothecin: CT, clinical trial
9 aminocamptothecin: AD, drug administration
9 aminocamptothecin: AN, drug analysis
9 aminocamptothecin: DV, drug development
9 aminocamptothecin: DO, drug dose
9 aminocamptothecin: DT, drug therapy
9 aminocamptothecin: PK, pharmacokinetics
9 aminocamptothecin: PD, pharmacology
9 aminocamptothecin: PO, oral drug administration
rebeccamycin: CT, clinical trial
rebeccamycin: AN, drug analysis
rebeccamycin: DV, drug development
rebeccamycin: DT, drug therapy
rebeccamycin: PK, pharmacokinetics
rebeccamycin: PD, pharmacology
losoxantrone: CT, clinical trial
losoxantrone: AN, drug analysis
losoxantrone: CB, drug combination
losoxantrone: DV, drug development
losoxantrone: DT, drug therapy
losoxantrone: PK, pharmacokinetics
losoxantrone: PD, pharmacology
methotrexate derivative: AN, drug analysis
methotrexate derivative: CB, drug combination
methotrexate derivative: DV, drug development
methotrexate derivative: DT, drug therapy
methotrexate derivative: PK, pharmacokinetics
methotrexate derivative: PD, pharmacology
tomudex: AN, drug analysis
tomudex: CB, drug combination
tomudex: DV, drug development
tomudex: DT, drug therapy
tomudex: PK, pharmacokinetics
tomudex: PD, pharmacology
lometrexol: AD, drug administration
lometrexol: AN, drug analysis
lometrexol: DV, drug development
lometrexol: DO, drug dose
lometrexol: DT, drug therapy
lometrexol: PK, pharmacokinetics
lometrexol: PD, pharmacology
lometrexol: IV, intravenous drug administration
fluorouracil derivative: AE, adverse drug reaction
fluorouracil derivative: AD, drug administration
fluorouracil derivative: AN, drug analysis
fluorouracil derivative: CB, drug combination
fluorouracil derivative: CM, drug comparison
fluorouracil derivative: DV, drug development
fluorouracil derivative: DT, drug therapy
fluorouracil derivative: PK, pharmacokinetics
fluorouracil derivative: PD, pharmacology
fluorouracil derivative: PO, oral drug administration
capecitabine: AE, adverse drug reaction
capecitabine: AD, drug administration
capecitabine: AN, drug analysis
capecitabine: CB, drug combination
capecitabine: CM, drug comparison
capecitabine: DV, drug development
capecitabine: DO, drug dose
capecitabine: DT, drug therapy
capecitabine: PK, pharmacokinetics
capecitabine: PD, pharmacology
capecitabine: PO, oral drug administration
5 ethynyluracil: AD, drug administration
5 ethynyluracil: CB, drug combination
5 ethynyluracil: CM, drug comparison
5 ethynyluracil: DO, drug dose
5 ethynyluracil: DT, drug therapy
5 ethynyluracil: PK, pharmacokinetics
5 ethynyluracil: PD, pharmacology
5 ethynyluracil: PO, oral drug administration
edelfosine: AE, adverse drug reaction
edelfosine: AN, drug analysis
edelfosine: DV, drug development
edelfosine: DO, drug dose
edelfosine: DT, drug therapy
edelfosine: PK, pharmacokinetics
edelfosine: PD, pharmacology
edelfosine: PO, oral drug administration
perifosine: AE, adverse drug reaction
perifosine: AN, drug analysis
perifosine: DV, drug development
perifosine: DO, drug dose
perifosine: DT, drug therapy
perifosine: PK, pharmacokinetics
perifosine: PD, pharmacology
perifosine: PO, oral drug administration
miltefosine: AN, drug analysis
miltefosine: DV, drug development
miltefosine: DT, drug therapy
miltefosine: PK, pharmacokinetics
miltefosine: PD, pharmacology
Vinca alkaloid: AN, drug analysis
Vinca alkaloid: DV, drug development
Vinca alkaloid: DT, drug therapy
Vinca alkaloid: PK, pharmacokinetics
Vinca alkaloid: PD, pharmacology
vinflunine: AN, drug analysis
vinflunine: DV, drug development
vinflunine: DT, drug therapy
vinflunine: PK, pharmacokinetics
vinflunine: PD, pharmacology
angiogenesis inhibitor: DV, drug development
fumagillol chloroacetylcarbamate: DV, drug development
marimastat: DV, drug development
thalidomide: DV, drug development
angiostatin: DV, drug development
unindexed drug
RN (temozolomide) 85622-93-1; (penclomedine) 108030-77-9; (rebeccamycin) 93908-02-2; (losoxantrone) 88303-60-0; (tomudex) 112887-68-0; (lometrexol) 106400-18-4, 106400-81-1, 120408-07-3, 95693-76-8; (capecitabine) 154361-50-9; (5 ethynyluracil) 59989-18-3; (edelfosine) 65492-82-2; (perifosine) 157716-52-4; (miltefosine) 58066-85-6; (vinflunine) 162652-95-1; (fumagillol chloroacetylcarbamate) 129298-91-5; (marimastat) 154039-60-8; (thalidomide)50-35-1; (angiostatin) 172642-30-7, 86090-08-6
CN Temodal; Ci 941; Zn d1694; Ly 264618; Xeloda; Miltex

L8 ANSWER 26 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2000218656 EMBASE
TI A review of current and future treatment strategies for malignant astrocytomas in adults.
AU Nieder C.; Nestle U.
CS Dr. U. Nestle, Abteilung fur Strahlentherapie, Radiologische

Universitatsklinik, D-66421 Homburg/Saar, Germany. raunes@med-rz.uni-saarland.de
SO Strahlentherapie und Onkologie, (2000) 176/6 (251-258).
Refs: 81
ISSN: 0179-7158 CODEN: STONE4
CY Germany
DT Journal; General Review
FS 016 Cancer
037 Drug Literature Index
LA English
SL English; German
AB Background: For more than 20 years, after establishing the role of postoperative radiotherapy for malignant astrocytomas, no definitive improvement in survival rates could be observed, despite advances in established treatment modalities such as radiotherapy and chemotherapy. This review discusses available laboratory and clinical data as well as recent advances in our knowledge about prognostic factors (Table 1) and their implications for the design of future clinical trials. Results: Elucidation of the biology of malignant astrocytomas allowed for development of rational new approaches, such as gene therapy and immunotherapy, which could interfere with established treatment regimens or being used independently. Possible strategies include the restoration of defective cancer-inhibitory genes, cell transduction or transfection with antisense DNA corresponding to genes coding for growth factors and their receptors, or with the so-called suicide genes. Several antiangiogenic approaches such as administration of thalidomide, protamine, or monoclonal antibodies against vascular endothelial growth factor have been developed, too. Further treatment possibilities include modulation of drug resistance, e.g. by P-glycoprotein antagonists or O6-alkyl-guanine-DNA-transferase inhibitors, inhibition of matrix metalloproteinases, inhibition of protein kinase C, and administration of agents such as phenylbutyrate or valproic acid that showed promising antiproliferative effects in vitro. Conclusions: Several rational new approaches are now entering clinical trials (Table 2). In the light of limited survival after standard treatment it is recommended that patients should be offered participation in such trials.
CT Medical Descriptors:
*astrocytoma: DR, drug resistance
*astrocytoma: DT, drug therapy
*astrocytoma: RT, radiotherapy
survival rate
prognosis
cancer inhibition
cell proliferation
gene therapy
quality of life
human
clinical trial
meta analysis
human tissue
human cell
adult
review
Drug Descriptors:
*thalidomide: CT, clinical trial
*thalidomide: DT, drug therapy
*thalidomide: PD, pharmacology
*protamine: CT, clinical trial
*protamine: DT, drug therapy
*protamine: PD, pharmacology
glycoprotein P: EC, endogenous compound
vasculotropin: EC, endogenous compound
matrix metalloproteinase inhibitor: CT, clinical trial
matrix metalloproteinase inhibitor: DT, drug therapy
matrix metalloproteinase inhibitor: PD, pharmacology
protein kinase inhibitor: CT, clinical trial
protein kinase inhibitor: DT, drug therapy
protein kinase inhibitor: PD, pharmacology
carmustine: CT, clinical trial
carmustine: DT, drug therapy
carmustine: PD, pharmacology
carmustine: IA, intraarterial drug administration
procarbazine: CT, clinical trial
procarbazine: DT, drug therapy
procarbazine: PD, pharmacology
procarbazine: IA, intraarterial drug administration
hydroxyurea: CT, clinical trial
hydroxyurea: DT, drug therapy
hydroxyurea: PD, pharmacology
hydroxyurea: IA, intraarterial drug administration
teniposide: CT, clinical trial
teniposide: DT, drug therapy
teniposide: PD, pharmacology
taxol: DT, drug therapy
topotecan: DT, drug therapy
irinotecan: DT, drug therapy
temozolomide: DT, drug therapy
2 chlorodeoxyadenosine: DT, drug therapy
eflornithine: DT, drug therapy
valproic acid: DT, drug therapy
leflunomide: DT, drug therapy
ag 3340: DT, drug therapy
RN (thalidomide) 50-35-1; (protamine) 11061-43-1, 9007-31-2, 9012-00-4; (vasculotropin) 127464-60-2; (carmustine) 154-93-8; (procarbazine) 366-70-1, 671-16-9; (hydroxyurea) 127-07-1; (teniposide) 29767-20-2; (taxol) 33069-62-4; (topotecan) 119413-54-6, 123948-87-8; (irinotecan) 100286-90-6; (temozolomide)85622-93-1; (2 chlorodeoxyadenosine) 4291-63-8; (eflornithine) 67037-37-0, 70052-12-9; (valproic acid) 1069-66-5, 99-66-1; (leflunomide) 75706-12-6; (ag 3340) 195008-93-6
CN Ag 3340

L8 ANSWER 27 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2000117710 EMBASE
TI Chemotherapy for high-grade gliomas.
AU Galanis E.; Buckner J.
CS E. Galanis, Division of Medical Oncology, Mayo Clinic and Foundation, 200 First Street SW, Rochester, MN 55905, United States
SO British Journal of Cancer, (2000) 82/8 (1371-1380).
Refs: 117
ISSN: 0007-0920 CODEN: BJCAAI
CY United Kingdom
DT Journal; General Review
FS 008 Neurology and Neurosurgery
016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
CT Medical Descriptors:
*glioma: DT, drug therapy
*glioma: RT, radiotherapy
*glioma: SU, surgery
blood toxicity: SI, side effect
brain disease: SI, side effect
cancer adjuvant therapy
cancer grading
cancer immunotherapy
cancer survival
gastrointestinal toxicity: SI, side effect
gene therapy
glioblastoma: DT, drug therapy
glioblastoma: RT, radiotherapy
glioblastoma: SU, surgery
oligodendroglioma: DT, drug therapy
side effect: SI, side effect
thromboembolism: SI, side effect
visual impairment: SI, side effect
human
clinical trial
phase 2 clinical trial
phase 3 clinical trial
review
priority journal
Drug Descriptors:
*antineoplastic agent: AE, adverse drug reaction
*antineoplastic agent: CT, clinical trial
*antineoplastic agent: AD, drug administration
*antineoplastic agent: CB, drug combination
*antineoplastic agent: CR, drug concentration
*antineoplastic agent: DT, drug therapy
*antineoplastic agent: PK, pharmacokinetics
*antineoplastic agent: IA, intraarterial drug administration
*antineoplastic agent: IV, intravenous drug administration
1 (2 chloroethyl) 3 (2,6 dioxo 3 piperidyl) 1 nitrosourea: AE, adverse drug reaction
1 (2 chloroethyl) 3 (2,6 dioxo 3 piperidyl) 1 nitrosourea: CT, clinical trial
1 (2 chloroethyl) 3 (2,6 dioxo 3 piperidyl) 1 nitrosourea: CB, drug combination
1 (2 chloroethyl) 3 (2,6 dioxo 3 piperidyl) 1 nitrosourea: DT, drug therapy
6 o benzylguanine: CT, clinical trial
6 o benzylguanine: CB, drug combination
6 o benzylguanine: DT, drug therapy
alpha interferon: CT, clinical trial
alpha interferon: CB, drug combination
alpha interferon: DT, drug therapy
angiogenesis inhibitor: CT, clinical trial
aziridinylbenzoquinone: CT, clinical trial
aziridinylbenzoquinone: CB, drug combination
aziridinylbenzoquinone: DT, drug therapy
carboplatin: CT, clinical trial
carboplatin: CB, drug combination
carboplatin: DT, drug therapy
carmustine: AE, adverse drug reaction
carmustine: CT, clinical trial
carmustine: AD, drug administration
carmustine: CB, drug combination
carmustine: DT, drug therapy
carmustine: IA, intraarterial drug administration
carmustine: IV, intravenous drug administration
chlormethine: CT, clinical trial
chlormethine: CB, drug combination
chlormethine: DT, drug therapy
cisplatin: AE, adverse drug reaction
cisplatin: CT, clinical trial
cisplatin: CB, drug combination
cisplatin: DT, drug therapy
cisplatin: IA, intraarterial drug administration
cisplatin: IV, intravenous drug administration
dacarbazine: CT, clinical trial
dacarbazine: CB, drug combination
dacarbazine: DT, drug therapy
fludarabine: CT, clinical trial
fludarabine: DT, drug therapy
fluorouracil: CT, clinical trial
fluorouracil: CB, drug combination
fluorouracil: DT, drug therapy
fluorouracil: IV, intravenous drug administration
hydroxyurea: CT, clinical trial
hydroxyurea: CB, drug combination
hydroxyurea: DT, drug therapy
irinotecan: CT, clinical trial
irinotecan: CR, drug concentration
irinotecan: DT, drug therapy
irinotecan: PK, pharmacokinetics
lomustine: CT, clinical trial
lomustine: CB, drug combination
lomustine: DT, drug therapy
misonidazole: CT, clinical trial
misonidazole: CB, drug combination
misonidazole: DT, drug therapy
mitolactol: CT, clinical trial
mitolactol: CB, drug combination
mitolactol: DT, drug therapy
nalpha [2 [arginylprolyl(4 hydroxyprolyl)glycyl[3 (2 thienyl)alanyl]serylprolylamino] 3 (4 methoxyphenyl)propyl]arginine: CT, clinical trial
nalpha [2 [arginylprolyl(4 hydroxyprolyl)glycyl[3 (2 thienyl)alanyl]serylprolylamino] 3 (4 methoxyphenyl)propyl]arginine: CB, drug combination
nalpha [2 [arginylprolyl(4 hydroxyprolyl)glycyl[3 (2 thienyl)alanyl]serylprolylamino] 3 (4 methoxyphenyl)propyl]arginine: DT, drug therapy
nalpha [2 [arginylprolyl(4 hydroxyprolyl)glycyl[3 (2 thienyl)alanyl]serylprolylamino] 3 (4 methoxyphenyl)propyl]arginine: IA, intraarterial drug administration
nalpha [2 [arginylprolyl(4 hydroxyprolyl)glycyl[3 (2 thienyl)alanyl]serylprolylamino] 3 (4 methoxyphenyl)propyl]arginine: IV, intravenous drug administration
nitrosourea: AE, adverse drug reaction
nitrosourea: CT, clinical trial
nitrosourea: AD, drug administration
nitrosourea: CB, drug combination
nitrosourea: DT, drug therapy
nitrosourea: IA, intraarterial drug administration
nitrosourea: IV, intravenous drug administration
procarbazine: CT, clinical trial
procarbazine: CB, drug combination
procarbazine: DT, drug therapy
retinoic acid: CT, clinical trial
retinoic acid: CB, drug combination
retinoic acid: DT, drug therapy
streptozocin: CT, clinical trial
streptozocin: CB, drug combination
streptozocin: DT, drug therapy
taxol: CT, clinical trial
taxol: DT, drug therapy
temozolomide: CT, clinical trial
temozolomide: CB, drug combination
temozolomide: DT, drug therapy
teniposide: CT, clinical trial
teniposide: DT, drug therapy
thalidomide: AE, adverse drug reaction
thalidomide: CT, clinical trial

thalidomide: DT, drug therapy
thiotepa: CT, clinical trial
thiotepa: CB, drug combination
thiotepa: DT, drug therapy
unindexed drug
vincristine: CT, clinical trial
vincristine: CB, drug combination
vincristine: DT, drug therapy
etoposide
fumagillol chloroacetylcarbamate
leflunomide

RN (1 (2 chloroethyl) 3 (2,6 dioxo 3 piperidyl) 1 nitrosourea) 13909-02-9; (6 o benzylguanine) 19916-73-5; (aziridinylbenzoquinone) 526-62-5; (carboplatin) 41575-94-4; (carmustine) 154-93-8; (chlormethine) 51-75-2, 55-86-7, 82905-71-3; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (dacarbazine) 4342-03-4; (fludarabine) 21679-14-1; (fluorouracil) 51-21-8; (hydroxyurea) 127-07-1; (irinotecan) 100286-90-6; (lomustine) 13010-47-4; (misonidazole) 13551-87-6; (mitolactol) 10318-26-0; (nalpha [2 [arginylprolyl(4 hydroxyprolyl)glycyl[3 (2 thienyl)alanyl]serylprolylamino] 3 (4 methoxyphenyl)propyl]arginine) 159768-75-9; (nitrosourea) 13010-20-3; (procarbazine) 366-70-1, 671-16-9; (retinoic acid) 302-79-4; (streptozocin) 18883-66-4; (taxol) 33069-62-4; (temozolomide) 85622-93-1; (teniposide) 29767-20-2; (thalidomide)50-35-1 ; (thiotepa) 52-24-4; (vincristine) 57-22-7; (etoposide) 33419-42-0; (fumagillol chloroacetylcarbamate) 129298-91-5; (leflunomide) 75706-12-6

CN Vp 16; Paclitaxel; Vm 26; Cpt 11; Rmp 7; Tnp 470; Su 101

L8 ANSWER 28 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 1999224768 EMBASE
TI New treatment strategies for malignant gliomas.
AU Avgeropoulos N.G.; Batchelor T.T.
CS Dr. N.G. Avgeropoulos, Massachusetts General Hospital, Brain Tumor Center, 100 Blossom Street, Boston, MA 02114, United States.
batchelor@helix.mgh.harvard.edu
SO Oncologist, (1999) 4/3 (209-224).
Refs: 126
ISSN: 1083-7159 CODEN: OCOLF6
CY United States
DT Journal; Article
FS 008 Neurology and Neurosurgery
016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LA English
SL English
AB Although survival in patients with malignant gliomas remains limited, there is renewed optimism with the emergence of novel treatment strategies. Cytotoxic agents such as temozolomide and CPT-11 have shown promising clinical activity. Biological treatments for brain tumors, including antisense oligonucleotides, gene therapy, and angiogenesis inhibitors, are also being evaluated in clinical trials. Delivery strategies have been developed to overcome challenges presented by the blood-brain barrier. These noteworthy treatments, alone or in combination, may ultimately prolong survival and enhance quality of life in this group of patients.
CT Medical Descriptors:
*glioblastoma: DT, drug therapy
*glioblastoma: TH, therapy
*astrocytoma: DT, drug therapy
*astrocytoma: TH, therapy
sensory neuropathy: SI, side effect
cancer immunotherapy
lymphokine activated killer cell
t lymphocyte
herpes simplex virus
retrovirus
drug delivery system
cancer survival
gene therapy
blood brain barrier
drug penetration
quality of life
drug structure
drug blood level
drug elimination
drug half life
bone marrow suppression: SI, side effect
gastrointestinal toxicity: SI, side effect
drug metabolism
fatigue: SI, side effect
alopecia: SI, side effect
human
nonhuman
clinical trial
oral drug administration
intravenous drug administration
article
priority journal
Drug Descriptors:
*cytotoxic agent: AE, adverse drug reaction
*cytotoxic agent: CT, clinical trial
*cytotoxic agent: DT, drug therapy
*antisense oligonucleotide: PD, pharmacology
*angiogenesis inhibitor: DT, drug therapy
*angiogenic factor: EC, endogenous compound
*anticonvulsive agent
*alkylating agent: AE, adverse drug reaction
*alkylating agent: CT, clinical trial
*alkylating agent: DT, drug therapy
polymer
placebo
carboplatin: PR, pharmaceutics
temozolomide: AE, adverse drug reaction
temozolomide: CT, clinical trial
temozolomide: AN, drug analysis
temozolomide: DT, drug therapy
temozolomide: PK, pharmacokinetics
temozolomide: PD, pharmacology
irinotecan: AE, adverse drug reaction
irinotecan: CT, clinical trial
irinotecan: AN, drug analysis
irinotecan: DT, drug therapy
irinotecan: PK, pharmacokinetics
topotecan: AE, adverse drug reaction
topotecan: CT, clinical trial
topotecan: AN, drug analysis
topotecan: DT, drug therapy
topotecan: PK, pharmacokinetics
9 aminocamptothecin: AE, adverse drug reaction
9 aminocamptothecin: CT, clinical trial
9 aminocamptothecin: DT, drug therapy
oxaliplatin: AE, adverse drug reaction
oxaliplatin: CT, clinical trial
oxaliplatin: AN, drug analysis
oxaliplatin: DT, drug therapy
protein kinase c inhibitor: PD, pharmacology
isis 3521: PD, pharmacology

tamoxifen: CT, clinical trial
tamoxifen: DT, drug therapy
tamoxifen: PD, pharmacology
staurosporine: PD, pharmacology
protein farnesyltransferase inhibitor: PD, pharmacology
cytokine: CT, clinical trial
cytokine: DT, drug therapy
recombinant alpha2a interferon: CT, clinical trial
recombinant alpha2a interferon: CB, drug combination
recombinant alpha2a interferon: DT, drug therapy
carmustine: CT, clinical trial
carmustine: CB, drug combination
carmustine: DT, drug therapy
carmustine: PR, pharmaceutics
interleukin 2
thymidine kinase: EC, endogenous compound
matrix metalloproteinase inhibitor: CT, clinical trial
matrix metalloproteinase inhibitor: DT, drug therapy
matrix metalloproteinase inhibitor: PD, pharmacology
marimastat: CT, clinical trial
marimastat: DT, drug therapy
marimastat: PD, pharmacology
thalidomide: CT, clinical trial
thalidomide: DT, drug therapy
thalidomide: PD, pharmacology
mannitol
nalpha [2 [arginylprolyl(4 hydroxyprolyl)glycyl[3 (2 thienyl)alanyl]serylprolylamino] 3 (4 methoxyphenyl)propyl]arginine: PD, pharmacology

RN (carboplatin) 41575-94-4; (temozolomide)85622-93-1; (irinotecan) 100286-90-6; (topotecan) 119413-54-6, 123948-87-8; (oxaliplatin) 61825-94-3; (isis 3521) 151879-73-1; (tamoxifen) 10540-29-1; (staurosporine) 62996-74-1; (carmustine) 154-93-8; (interleukin 2) 85898-30-2; (thymidine kinase) 9002-06-6, 9086-73-1; (marimastat) 154039-60-8; (thalidomide)50-35-1; (mannitol) 69-65-8, 87-78-5; (nalpha [2 [arginylprolyl(4 hydroxyprolyl)glycyl[3 (2 thienyl)alanyl]serylprolylamino] 3 (4 methoxyphenyl)propyl]arginine) 159768-75-9

CN Isis 3521; Rmp 7

L8 ANSWER 29 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 1999173684 EMBASE
TI New chemotherapy options for the treatment of malignant gliomas.
AU Burton E.; Prados M.
CS Dr. E. Burton, Department of Neurosurgery, M787, San Francisco, CA 94143-0112, United States
SO Current Opinion in Oncology, (1999) 11/3 (157-161).
Refs: 24
ISSN: 1040-8746 CODEN: CUOOE8
CY United States
DT Journal; General Review
FS 008 Neurology and Neurosurgery
016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Chemotherapy remains part of the treatment triad that includes surgery and radiation therapy for the management of malignant gliomas. In recent years there has been an increased understanding of the molecular pathways of malignant transformation. Based on this research, new drugs have been evaluated, with specific cellular targets in mind that can be modified or inhibited. Many of these agents are now being tested in phase I and II clinical trials and have shown some promising results. Clearly, not all patients with malignant gliomas respond equally to chemotherapy. Recent evidence suggests that certain molecular markers may predict chemosensitivity in some tumor types, particularly anaplastic oligodendroglioma. This article reviews recent trends in the use of chemotherapy and clinical trials of new therapies for adults with malignant gliomas.
CT Medical Descriptors:
*glioblastoma: DT, drug therapy
*glioblastoma: RT, radiotherapy
*glioblastoma: SU, surgery
malignant transformation
drug targeting
phase 1 clinical trial
phase 2 clinical trial
human
clinical trial
review
priority journal
Drug Descriptors:
*antineoplastic agent: CT, clinical trial
*antineoplastic agent: DT, drug therapy
*antineoplastic agent: PD, pharmacology
biological marker: EC, endogenous compound
new drug: CT, clinical trial
new drug: DT, drug therapy
new drug: PD, pharmacology
carmustine: CT, clinical trial
carmustine: CB, drug combination
carmustine: DT, drug therapy
procarbazine: CT, clinical trial
procarbazine: CB, drug combination
procarbazine: DT, drug therapy
lomustine: CT, clinical trial
lomustine: CB, drug combination
lomustine: DT, drug therapy
vincristine: CT, clinical trial
vincristine: CB, drug combination
vincristine: DT, drug therapy
carboplatin: CT, clinical trial
carboplatin: DT, drug therapy
cisplatin: CT, clinical trial
cisplatin: DT, drug therapy
tamoxifen: CT, clinical trial
tamoxifen: DT, drug therapy
temozolomide: CT, clinical trial
temozolomide: DT, drug therapy
irinotecan: CT, clinical trial
irinotecan: DT, drug therapy
tetrazine derivative: CT, clinical trial
tetrazine derivative: DT, drug therapy
leflunomide: CT, clinical trial
leflunomide: CB, drug combination
leflunomide: DT, drug therapy
7 hydroxystaurosporine: CT, clinical trial
7 hydroxystaurosporine: DT, drug therapy
suramin: CT, clinical trial
suramin: DT, drug therapy
matrix metalloproteinase inhibitor: CT, clinical trial
matrix metalloproteinase inhibitor: DT, drug therapy
angiogenesis inhibitor: CT, clinical trial
angiogenesis inhibitor: DT, drug therapy
thalidomide: CT, clinical trial
thalidomide: DT, drug therapy
thrombocyte factor 4: CT, clinical trial

thrombocyte factor 4: DT, drug therapy
interleukin 12: CT, clinical trial
interleukin 12: DT, drug therapy
alpha interferon: CT, clinical trial
alpha interferon: DT, drug therapy
fumagillol chloroacetylcarbamate: CT, clinical trial
fumagillol chloroacetylcarbamate: DT, drug therapy
RN (carmustine) 154-93-8; (procarbazine) 366-70-1, 671-16-9; (lomustine) 13010-47-4; (vincristine) 57-22-7; (carboplatin) 41575-94-4; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (tamoxifen) 10540-29-1; (temozolomide) 85622-93-1; (irinotecan) 100286-90-6; (leflunomide) 75706-12-6; (7 hydroxystaurosporine) 112953-11-4; (suramin) 129-46-4, 145-63-1; (thalidomide) 50-35-1; (thrombocyte factor 4) 37270-94-3, 69670-74-2; (interleukin 12) 138415-13-1; (fumagillol chloroacetylcarbamate) 129298-91-5
CN Cpt 11; Su 101; Ucn 01; Tnp 470

L8 ANSWER 30 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 1999069770 EMBASE
TI Innovative therapies for pediatric brain tumors.
AU Rubin J.B.; Kieran M.W.
CS Dr. J.B. Rubin, Dana Farber Cancer Institute, Department of Pediatric Oncology, 44 Binney Street, Boston, MA 02115, United States
SO Current Opinion in Pediatrics, (1999) 11/1 (39-46).
Refs: 143
ISSN: 1040-8703 CODEN: COPEE
CY United States
DT Journal; General Review
FS 007 Pediatrics and Pediatric Surgery
014 Radiology
016 Cancer
022 Human Genetics
026 Immunology, Serology and Transplantation
027 Biophysics, Bioengineering and Medical Instrumentation
030 Pharmacology
037 Drug Literature IndexPharmacology
LA English
SL English
AB Success in the treatment of pediatric brain tumors has lagged behind that of other pediatric cancers. This paper highlights many of the advances that have taken place over the past few years in the surgical, radiotherapeutic, and chemotherapeutic approaches to central nervous system lesions that we hope will lead to a dramatic improvement in outcome. Innovations in neurosurgical and radiotherapeutic techniques have resulted in decreasing toxicity although substantial improvement in cure rates has not been observed. Many new techniques such as gene therapy, angiogenesis inhibitors, immunotherapy, and others that have not been part of the classic approach to these lesions are now in clinical trials in the hope that they will impact on the survival of these patients. The scientific basis for these new treatment modalities and preliminary clinical results are discussed.
CT Medical Descriptors:
*brain tumor: DT, drug therapy
*brain tumor: RT, radiotherapy
*brain tumor: SU, surgery
*brain tumor: TH, therapy
central nervous system tumor: DT, drug therapy
central nervous system tumor: RT, radiotherapy
central nervous system tumor: SU, surgery
central nervous system tumor: TH, therapy
gene therapy
angiogenesis
immunotherapy
neurosurgery
nuclear magnetic resonance imaging
brachytherapy
dosimetry
proton radiation
stereotaxic surgery
human
infant
child
review
priority journal
Drug Descriptors:
angiogenesis inhibitor: DT, drug therapy
misonidazole: DV, drug development
misonidazole: DT, drug therapy
etanidazole: DV, drug development
etanidazole: DT, drug therapy
broxuridine: CT, clinical trial
broxuridine: DT, drug therapy
cisplatin: DT, drug therapy
iodine 125: DT, drug therapy
iodine 125: TO, drug toxicity
iridium 192: DT, drug therapy
iridium 192: TO, drug toxicity
metalloproteinase inhibitor: DV, drug development
metalloproteinase inhibitor: DT, drug therapy
fumagillol chloroacetylcarbamate: DV, drug development
fumagillol chloroacetylcarbamate: DT, drug therapy
thalidomide: CT, clinical trial
thalidomide: DT, drug therapy
alpha interferon: CT, clinical trial
alpha interferon: DT, drug therapy
vitaxin
tenascin: EC, endogenous compound
antineoplastic agent: DV, drug development
antineoplastic agent: DT, drug therapy
arylbutyric acid derivative: DV, drug development
arylbutyric acid derivative: DT, drug therapy
phenylacetic acid: DV, drug development
phenylacetic acid: DT, drug therapy
ganglioside gm3: DV, drug development
ganglioside gm3: DT, drug therapy
nalpha [2 [arginylprolyl[4 hydroxyprolyl]glycyl[3 (2 thienyl)alanyl]serylprolylamino] 3 (4 methoxyphenyl]propyl]arginine: DT, drug therapy
temozolomide: DV, drug development
temozolomide: DT, drug therapy
RN (misonidazole) 13551-87-6; (etanidazole) 22668-01-5; (broxuridine) 59-14-3; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (iodine 125) 14158-31-7, 22822-81-7; (iridium 192) 14694-69-0; (fumagillol chloroacetylcarbamate) 129298-91-5; (thalidomide) 50-35-1; (phenylacetic acid) 103-82-2; (ganglioside gm3) 54827-14-4; (nalpha [2 [arginylprolyl[4 hydroxyprolyl]glycyl[3 (2 thienyl)alanyl]serylprolylamino] 3 (4 methoxyphenyl)propyl]arginine) 159768-75-9; (temozolomide) 85622-93-1
CN Tnp 470; Vitaxin; Rmp 7
CO Ixsys (United States); Schering Plough (United States)

L8 ANSWER 31 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 1998341815 EMBASE
TI New frontiers in therapy of malignant gliomas.
AU Puduvalli V.K.; Yung W.K.A.
CS W.K.A. Yung, Department of Neuro-oncology, The University of Texas, M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, United States
SO FORUM - Trends in Experimental and Clinical Medicine, (1998) 8/3 (261-269).
Refs: 89
ISSN: 1121-8142 CODEN: FTCME2
CY Italy
DT Journal; General Review
FS 008 Neurology and Neurosurgery
016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB The prognosis of patients with malignant gliomas remains dismal despite the development of a multidisciplinary approach to their treatment. There is a strong need for novel therapeutic approaches that can make a definite impact in the clinical course of these tumours. Although there have been several advances in diagnostic modalities, surgical techniques and cytotoxic therapies, the development of newer therapies has been hampered by the limited understanding of the factors that determine the biological nature of gliomas. However, inroads are now being made into the understanding of the genetic make-up, biological behaviour and therapeutic response of these tumours, which are expected to pave the way for new modes of treatment. In this article, we review the advances made in the identification of potential targets for glioma therapy and the recent clinical trials utilising biological therapies and newer cytotoxic agents.
CT Medical Descriptors:
*glioblastoma: DI, diagnosis
*glioblastoma: DT, drug therapy
*glioblastoma: SU, surgery
*glioblastoma: TH, therapy
prognosis
disease course
diagnostic procedure
surgical technique
biological therapy
angiogenesis
teratogenicity: SI, side effect
side effect
cancer invasion
gene therapy
human
nonhuman
oral drug administration
clinical trial
review
Drug Descriptors:
cytotoxic agent: DT, drug therapy
antineoplastic agent: CT, clinical trial
antineoplastic agent: DT, drug therapy
thalidomide: AE, adverse drug reaction
thalidomide: CT, clinical trial
thalidomide: DT, drug therapy
fumigillin: AE, adverse drug reaction
fumigillin: CT, clinical trial
fumigillin: DT, drug therapy
fumagillol chloroacetylcarbamate: CT, clinical trial
fumagillol chloroacetylcarbamate: DT, drug therapy
angiogenesis inhibitor: AE, adverse drug reaction
angiogenesis inhibitor: DT, drug therapy
angiostatin: CT, clinical trial
angiostatin: DT, drug therapy
thrombocyte factor 4: CT, clinical trial
thrombocyte factor 4: DT, drug therapy
marimastat: CT, clinical trial
marimastat: AD, drug administration
marimastat: DT, drug therapy
ag 3340: CT, clinical trial
ag 3340: DT, drug therapy
eflornithine: CT, clinical trial
eflornithine: CB, drug combination
eflornithine: DT, drug therapy
lomustine: CT, clinical trial
lomustine: CB, drug combination
lomustine: DT, drug therapy
procarbazine: CT, clinical trial
procarbazine: CB, drug combination
procarbazine: DT, drug therapy
vincristine: CT, clinical trial
vincristine: CB, drug combination
vincristine: DT, drug therapy
retinoid: AD, drug administration
retinoid: DT, drug therapy
temozolomide: CT, clinical trial
temozolomide: DT, drug therapy
topotecan: CT, clinical trial
topotecan: DT, drug therapy
irinotecan: CT, clinical trial
irinotecan: DT, drug therapy
unclassified drug
RN (thalidomide) 50-35-1; (fumagillol chloroacetylcarbamate) 129298-91-5; (angiostatin) 172642-30-7, 86090-08-6; (thrombocyte factor 4) 37270-94-3, 69670-74-2; (marimastat) 154039-60-8; (eflornithine) 67037-37-0, 70052-12-9; (lomustine) 13010-47-4; (procarbazine) 366-70-1, 671-16-9; (vincristine) 57-22-7; (temozolomide) 85622-93-1; (topotecan) 119413-54-6, 123948-87-8; (irinotecan) 100286-90-6
CN Tnp 470; Ag 3340

L8 ANSWER 32 OF 40 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 97049528 EMBASE
DN 1997049528
TI Recognition and management of gliomas.
AU Kaba S.E.; Kyritsis A.P.
CS Dr. S.E. Kaba, Department of Neurology, UAMS, 4301 W. Markham Street, Little Rock, AR 72205, United States
SO Drugs, (1997) 53/2 (235-244).
Refs: 56
ISSN: 0012-6667 CODEN: DRUGAY
CY New Zealand
DT Journal; General Review
FS 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Gliomas are the most frequent primary brain tumours. They include astrocytic gliomas, oligodendrocytic gliomas, ependymomas and gliomas with mixed cell populations. Each glioma type consists of both low-grade and malignant atypical varieties. The low-grade rumours occur predominantly in children and young adults, and the malignant forms in older people. The presenting symptoms are epileptic seizures, headache and mental confusion. Focal neurological symptoms and findings, such as hemiparesis, are mostly associated with the malignant forms. Magnetic resonance imaging (MRI) scan of the brain with and without gadolinium contrast demonstrates the tumour. However, stereotactic biopsy or surgical resection is necessary to obtain the correct pathological diagnosis, except for diffuse pontine astrocytomas, which have an unmistakeable imaging appearance and for which biopsy has substantial risks. Treatment depends on the pathological diagnosis. Complete surgical resection may be curative for low-grade

tumours. Postoperative radiotherapy is recommended for partially resected rumours. Most malignant gliomas require aggressive combination therapy with radiotherapy and chemotherapy after maximal surgery. The standard initial regimens are nitrosourea-based chemotherapies, such as carmustine alone, a combination of procarbazine, lomustine and vincristine, or a combination of thioguanine, procarbazine, lomustine and hydroxycarbamide (hydroxyurea). Unfortunately, the prognosis of malignant gliomas is generally poor despite aggressive treatment, because of their infiltrative nature and high relapse rate.

CT Medical Descriptors:
*glioma: DI, diagnosis
*glioma: SU, surgery
*glioma: RT, radiotherapy
*glioma: DT, drug therapy
astrocytoma: DI, diagnosis
astrocytoma: SU, surgery
astrocytoma: DT, drug therapy
astrocytoma: RT, radiotherapy
brain biopsy
brain stem tumor: DI, diagnosis
brain stem tumor: RT, radiotherapy
brain stem tumor: DT, drug therapy
brain surgery
brain tumor: SU, surgery
brain tumor: RT, radiotherapy
brain tumor: DT, drug therapy
brain tumor: DI, diagnosis
cancer infiltration
cancer recurrence
cancer surgery
clinical trial
ependymoma: RT, radiotherapy
ependymoma: SU, surgery
ependymoma: DT, drug therapy
ependymoma: DI, diagnosis
headache
hemiparesis
human
intravenous drug administration
mental disease
neurologic disease
nuclear magnetic resonance imaging
oligodendroglioma: SU, surgery
oligodendroglioma: RT, radiotherapy
oligodendroglioma: DT, drug therapy
oligodendroglioma: DI, diagnosis
oral drug administration
prognosis
review
seizure
symptom
Drug Descriptors:
alpha interferon: DT, drug therapy
alpha interferon: CT, clinical trial
arylbutyric acid derivative: DT, drug therapy
arylbutyric acid derivative: CT, clinical trial
beta interferon: CT, clinical trial
beta interferon: DT, drug therapy
carboplatin: CB, drug combination
carboplatin: DT, drug therapy
carmustine: DT, drug therapy
corticosteroid: DT, drug therapy
etoposide: CB, drug combination
etoposide: DT, drug therapy
fluorouracil: DT, drug therapy
fluorouracil: CB, drug combination
fumagillol chloroacetylcarbamate: DT, drug therapy
fumagillol chloroacetylcarbamate: CT, clinical trial
gadolinium
hydroxyurea: CB, drug combination
hydroxyurea: DT, drug therapy
isotretinoin: CT, clinical trial
isotretinoin: DT, drug therapy
lomustine: DT, drug therapy
lomustine: CB, drug combination
monoclonal antibody: DT, drug therapy
monoclonal antibody: CT, clinical trial
phenylacetic acid: DT, drug therapy
phenylacetic acid: CT, clinical trial
procarbazine: DT, drug therapy
procarbazine: CB, drug combination
tamoxifen: DT, drug therapy
tamoxifen: CT, clinical trial
temozolomide: CT, clinical trial
temozolomide: DT, drug therapy
thalidomide: DT, drug therapy
thalidomide: CT, clinical trial
tioguanine: CB, drug combination
tioguanine: DT, drug therapy
topotecan: CT, clinical trial
topotecan: DT, drug therapy
vincristine: CB, drug combination
vincristine: DT, drug therapy

RN (carboplatin) 41575-94-4; (carmustine) 154-93-8; (etoposide) 33419-42-0; (fluorouracil) 51-21-8; (fumagillol chloroacetylcarbamate) 129298-91-5; (gadolinium) 7440-54-2; (hydroxyurea) 127-07-1; (isotretinoin) 4759-48-2; (lomustine) 13010-47-4; (phenylacetic acid) 103-82-2; (procarbazine) 366-70-1, 671-16-9; (tamoxifen) 10540-29-1; (temozolomide) 85622-93-1; (thalidomide) 50-35-1; (tioguanine) 154-42-7; (topotecan) 119413-54-6, 123948-87-8; (vincristine) 57-22-7
CN Agm 1470

L8 ANSWER 33 OF 40 MEDLINE
AN 2001192567 MEDLINE
DN 21075767 PubMed ID: 11204670
TI New approaches in the treatment of metastatic melanoma: thalidomide and temozolomide.
AU Hwu W J
CS Memorial Sloan-Kettering Cancer Center, New York, New York, USA.
SO ONCOLOGY, (2000 Dec) 14 (12 Suppl 13) 25-8. Ref: 16
Journal code: 8712059. ISSN: 0890-9091.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200104
ED Entered STN: 20010410
Last Updated on STN: 20010410
Entered Medline: 20010405
AB Although melanoma is a relatively chemoresistant malignancy, systemic chemotherapy remains the primary treatment for metastatic melanoma. The observation of vasculogenic mimicry in aggressive melanoma has prompted investigation into using an antiangiogenic agent to enhance the antitumor activity of chemotherapy in metastatic melanoma. Thalidomide (Thalomid) exhibits antiangiogenic activity and other biological modulatory effects that may provide additive or synergistic antitumor effects when given concurrently with chemotherapy. A phase I/II study of thalidomide and temozolomide in the treatment of metastatic melanoma is in progress. Preliminary results of this combination therapy have shown significant antitumor activity, including some striking responses in brain metastases.
CT Check Tags: Case Report; Female; Human; Male
Adult
*Angiogenesis Inhibitors: TU, therapeutic use
*Antineoplastic Agents, Alkylating: TU, therapeutic use
*Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use
Clinical Trials, Phase I
Clinical Trials, Phase II
*Dacarbazine: AA, analogs & derivatives
*Dacarbazine: TU, therapeutic use
*Melanoma: DT, drug therapy
Middle Age
Neoplasm Metastasis
*Thalidomide: TU, therapeutic use
RN 4342-03-4 (Dacarbazine); 50-35-1 (Thalidomide); 85622-93-1 (temozolomide)
CN 0 (Angiogenesis Inhibitors); 0 (Antineoplastic Agents, Alkylating); 0 (Antineoplastic Combined Chemotherapy Protocols)

L8 ANSWER 34 OF 40 MEDLINE
AN 1999259140 MEDLINE
DN 99259140 PubMed ID: 10328588
TI New chemotherapy options for the treatment of malignant gliomas.
AU Burton E; Prados M
CS University of California, San Francisco, Department of Neurosurgery, USA.
NC CA09291 (NCI)
CA13525 (NCI)
SO CURRENT OPINION IN ONCOLOGY, (1999 May) 11 (3) 157-61. Ref: 24
Journal code: 9007265. ISSN: 1040-8746.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals; AIDS
EM 199906
ED Entered STN: 19990714
Last Updated on STN: 19990714
Entered Medline: 19990628
AB Chemotherapy remains part of the treatment triad that includes surgery and radiation therapy for the management of malignant gliomas. In recent years there has been an increased understanding of the molecular pathways of malignant transformation. Based on this research, new drugs have been evaluated, with specific cellular targets in mind that can be modified or inhibited. Many of these agents are now being tested in phase I and II clinical trials and have shown some promising results. Clearly, not all patients with malignant gliomas respond equally to chemotherapy. Recent evidence suggests that certain molecular markers may predict chemosensitivity in some tumor types, particularly anaplastic oligodendroglioma. This article reviews recent trends in the use of chemotherapy and clinical trials of new therapies for adults with malignant gliomas.
CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
Adult
*Antineoplastic Agents: TU, therapeutic use
*Brain Neoplasms: DT, drug therapy
Brain Neoplasms: PP, physiopathology
Camptothecin: AA, analogs & derivatives
Camptothecin: TU, therapeutic use
Clinical Trials
Dacarbazine: AA, analogs & derivatives
Dacarbazine: TU, therapeutic use
Enzyme Inhibitors: TU, therapeutic use
*Glioma: DT, drug therapy
Glioma: PP, physiopathology
Neovascularization, Pathologic: PC, prevention & control
Oligodendroglioma: DT, drug therapy
Oligodendroglioma: GE, genetics
Protease Inhibitors: TU, therapeutic use
Signal Transduction: PH, physiology
Thalidomide: TU, therapeutic use
RN 100286-90-6 (irinotecan); 4342-03-4 (Dacarbazine); 50-35-1 (Thalidomide); 7689-03-4 (Camptothecin); 85622-93-1 (temozolomide)
CN 0 (Antineoplastic Agents); 0 (Enzyme Inhibitors); 0 (Protease Inhibitors)

L8 ANSWER 35 OF 40 TOXCENTER COPYRIGHT 2003 ACS
AN 2001:30005 TOXCENTER
DN 21075767 PubMed ID: 11204670
TI New approaches in the treatment of metastatic melanoma: thalidomide and temozolomide
AU Hwu W J
CS Memorial Sloan-Kettering Cancer Center, New York, New York, USA
SO ONCOLOGY, (2000 Dec) 14 (12 Suppl 13) 25-8. Ref: 16.
Journal Code: 8712059. ISSN: 0890-9091.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
FS MEDLINE
OS MEDLINE 2001192567
LA English
ED Entered STN: 20011116
Last Updated on STN: 20011116
AB Although melanoma is a relatively chemoresistant malignancy, systemic chemotherapy remains the primary treatment for metastatic melanoma. The observation of vasculogenic mimicry in aggressive melanoma has prompted investigation into using an antiangiogenic agent to enhance the antitumor activity of chemotherapy in metastatic melanoma. Thalidomide (Thalomid) exhibits antiangiogenic activity and other biological modulatory effects that may provide additive or synergistic antitumor effects when given concurrently with chemotherapy. A phase I/II study of thalidomide and temozolomide in the treatment of metastatic melanoma is in progress. Preliminary results of this combination therapy have shown significant antitumor activity, including some striking responses in brain metastases.
CT Check Tags: Case Report; Female; Human; Male
Adult
*Angiogenesis Inhibitors: TU, therapeutic use
*Antineoplastic Agents, Alkylating: TU, therapeutic use
*Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use
Clinical Trials, Phase I
Clinical Trials, Phase II
*Dacarbazine: AA, analogs & derivatives
*Dacarbazine: TU, therapeutic use
*Melanoma: DT, drug therapy
Middle Age
Neoplasm Metastasis
*Thalidomide: TU, therapeutic use
RN 4342-03-4 (Dacarbazine)
50-35-1 (Thalidomide)
85622-93-1 (temozolomide)
CN 0 (Angiogenesis Inhibitors); 0 (Antineoplastic Agents, Alkylating); 0 (Antineoplastic Combined Chemotherapy Protocols)

L8 ANSWER 36 OF 40 TOXCENTER COPYRIGHT 2003 ACS

AN 2000:168159 TOXCENTER
CP Copyright 2003 ACS
DN CA133081099496
TI Pharmaceutical compositions for treatment of diseased tissues
AU Lee, Clarence C.; Lee, Feng-Min
PI WO 2000040269 A2 13 Jul 2000
SO (2000) PCT Int. Appl., 26 pp.
CODEN: PIXXD2.
CY UNITED STATES
DT Patent
FS CAPLUS
OS CAPLUS 2000:475560
LA English
ED Entered STN: 20011116
Last Updated on STN: 20020326
AB A method to treat diseased tissue is provided where a cytotoxic compd. is administered to a patient in need of treatment in combination with an immunostimulant. Diseased cells and/or infectious microbes/viruses are killed by the cytotoxic compd. in the presence of the immunostimulant. The cell components including cellular contents and cell membrane fragments are presented by the immunostimulant to the host animal as antigens to stimulate the immune responses toward other diseased cells of the same type(s), that either remain in the vicinity or reside in distant tissues or organs. The cytotoxic mol. and immunostimulant are preferably applied locally at high concns., either sequentially or, preferably, simultaneously. For example, the compn. can be administered directly to a target cancer. The compn. can be prepd. in various forms, such as a paste, a time release molded solid shape, a soln., a mixt. with emulsifier, etc. Alternatively, the cytotoxic mol. and immunostimulant are applied in sequence.
CC 63-6
ST Miscellaneous Descriptors
antitumor immunostimulant antigen formulation local delivery
RN 62488-57-7 (DHAC)
9041-38-7Q (Teichoic acid, lipo-)
14769-73-4 (Levamisole)
50-35-1 (Thalidomide)
50-76-0 (Dactinomycin)
50-81-7 (Ascorbic acid)
51-21-8 (5-Fluorouracil)
51-79-6 (Urethan)
52-67-5 (Penicillamine)
53-19-0 (Mitotane)
54-42-2 (Idoxuridine)
54-62-6 (Aminopterin)
55-86-7 (Nitrogen mustard)
56-53-1 (Diethylstilbestrol)
56-75-7Q (Amphenicol, derivs.)
58-40-2 (Prazine)
59-14-3 (Budr)
59-30-3Q (Folic acid, analogs)
60-00-4 (Edta)
60-54-8Q (Tetracycline, derivs.)
62-33-9 (Calcium disodium edetate)
64-02-8 (Sodium edetate)
64-18-6 (Formic acid)
64-19-7 (Acetic acid)
67-43-6 (Pentetic acid)
67-63-0 (Isopropanol)
67-68-5 (Dmso)
68-76-8 (Triaziquone)
69-33-0 (Tubercidin)
70-51-9 (Deferoxamine)
73-03-0 (Cordycepin)
75-75-2Q (Methanesulfonic acid, derivs.)
120-73-0Q (Purine, analogs)
122-79-2 (Phenylacetate)
127-07-1 (Hydroxyurea)
127-07-1Q (Hydroxyurea, derivs.)
139-33-3 (Disodium edetate)
150-38-9 (Trisodium edetate)
151-56-4 (Aziridine)
289-95-2Q (Pyrimidine, analogs)
302-79-4 (Tretinoin)
304-55-2 (Succimer)
320-67-2 (5-Azacytidine)
366-70-1 (Matulane)
459-86-9 (Mitoguazone)
477-30-5 (Demecolcine)
518-28-5 (Podophyllotoxin)
569-57-3 (Chlorotrianisene)
636-47-5 (Stallimycin)
642-83-1 (Aceglatone)
645-05-6 (Altretamine)
671-16-9 (Procarbazine)
768-94-5 (Amantadine)
801-52-5 (Porfiromycin)
1174-11-4 (Xenazoic acid)
1310-73-2 (Sodium hydroxide)
1402-44-4 (Actinomycin F1)
1404-00-8Q (Mitomycin, derivs.)
1508-45-8 (Podophyllinic acid 2-ethylhydrazide)
1910-68-5 (Methisazone)
1954-28-5 (Etoglucid)
3572-60-9 (Amidinomycin)
3731-59-7 (Moroxydine)
3733-81-1 (Defosfamide)
3819-34-9 (Phenamet)
3930-19-6 (Streptonigrin)
4533-39-5 (Nitracrine)
4803-27-4 (Anthramycin)
5300-03-8 (9-cis-Retinoic acid)
7440-06-4Q (Platinum, complexes)
7647-01-0 (Hydrochloric acid)
7647-17-8 (Cesium chloride)
7664-93-9 (Sulfuric acid)
7761-88-8 (Silver nitrate)
9001-63-2 (Lysozyme)
9014-02-2 (Zinostatin)
9015-68-3 (Asparaginase)
10318-26-0 (Mitolactol)
11006-77-2 (Statolon)
11056-06-7Q (Bleomycin, derivs.)
12111-24-9 (Calcium trisodium pentetate)
13010-20-3Q (Nitrosourea, derivs.)
13311-84-7 (Flutamide)
13392-28-4 (Rimantadine)
13494-90-1 (Gallium nitrate)
13665-88-8 (Mopidamol)
15663-27-1 (Cisplatin)
18378-89-7 (Plicamycin)
20537-88-6 (Amifostine)
20830-81-3 (Daunorubicin)
21416-67-1 (Razoxane)
22668-01-5 (Radinyl)
23214-92-8 (Doxorubicin)
24967-93-9 (Chondroitin sulfate A)
26657-95-4 (Dipalmitoylglycerol)
26833-87-4 (Homoharringtonine)
27314-97-2 (Tirapazamine)
27762-78-3 (Kethoxal)
27778-66-1 (Tenuazonic acid)
29767-20-2 (Teniposide)
33069-62-4 (Paclitaxel)
33419-42-0 (Etoposide)
36703-88-5 (Isoprinosine)
36791-04-5 (Ribavirin)
38819-10-2 (Guanine arabinoside)
39389-47-4 (Distamycin)
41992-23-8 (Spirogermanium)
50264-69-2 (Lonidamine)
51264-14-3 (Amsacrine)
52205-73-9 (Estramustine phosphate sodium)
53678-77-6 (Muramyl dipeptide)
53783-83-8 (Tromantadine)
53910-25-1 (Pentostatin)
56741-95-8 (Bropirimine)
57998-68-2 (Diaziquone)
58066-85-6 (Miltefosine)
58337-35-2 (Elliptinium acetate)
58957-92-9 (Idarubicin)
61825-94-3 (Oxaliplatin)
63585-09-1 (Foscarnet sodium)
63612-50-0 (Nilutamide)
65271-80-9 (Mitoxantrone)
65646-68-6 (Fenretinide)
66676-88-8Q (Aclacinomycin, derivs.)
70052-12-9 (Eflornithine)
72732-56-0 (Piritrexim)
74913-06-7Q (Chromomycin, derivs.)
75706-12-6 (SU101)
78186-34-2 (Bisantrene)
80738-43-8Q (Lincosamide, derivs.)
82413-20-5 (Droloxifene)
82952-64-5 (Trimetrexate glucuronate)
83314-01-6 (Bryostatin 1)
84088-42-6 (Linomide)
85622-93-1 (Temozolomide)
89778-26-7 (Toremifene)
95058-81-4 (Gemcitabine)
96389-68-3 (Crisnatol)
97682-44-5 (Irinotecan)
98631-95-9 (Sobuzoxane)
107868-30-4 (Exemestane)
110042-95-0 (Acemannan)
110314-48-2 (Adozelesin)
112809-51-5 (Letrozole)
114977-28-5 (Docetaxel)
115575-11-6 (Liarozole)
116057-75-1 (Idoxifene)
120511-73-1 (Anastrozole)
121181-53-1 (Filgrastim)
123948-87-8 (Topotecan)
125317-39-7 (Navelbine)
126268-81-3 (CI-980)
127779-20-8 (Saquinavir)
129618-40-2 (Nevirapine)
129655-21-6 (Bizelesin)
133432-71-0 (Peldesine)
135467-16-2 (Octreotide pamoate)
136817-59-9 (Delavirdine)
144849-63-8 (Bisnafide)
150378-17-9 (Indinavir)
154361-50-9 (Capecitabine)
155213-67-5 (Ritonavir)
159768-75-9 (RMP-7)
159997-94-1 (VX-710)
RN 112-24-3; 121-76-6; 2353-33-5; 74853-75-1; 97919-22-7; 98930-34-8; 282102-49-2; 282102-50-5; 282527-39-3; 282527-40-6

L8 ANSWER 37 OF 40 TOXCENTER COPYRIGHT 2003 ACS
AN 1999:208077 TOXCENTER
CP Copyright 2003 ACS
DN CA13126346535K
TI Use of neomycin for treating angiogenesis-related diseases
AU Hu, Guo-Fu; Vallee, Bert L.
CS ASSIGNEE: The Endowment for Research In Human Biology, Inc.
PI WO 9958126 A1 18 Nov 1999
SO (1999) PCT Int. Appl., 74 pp.
CODEN: PIXXD2.
CY UNITED STATES
DT Patent
FS CAPLUS
OS CAPLUS 1999:736476
LA English
ED Entered STN: 20011116
Last Updated on STN: 20030225
AB The present invention is directed to using neomycin or an analog thereof as a therapeutic agent to treat angiogenesis-related diseases, which are characterized by excessive, undesired or inappropriate angiogenesis or proliferation of endothelial cells. The present invention is also directed to pharmaceutical comps. comprising: (a) neomycin or an analog and, optionally, (b) another anti-angiogenic agent or an anti-neoplastic agent. The present invention is further directed to a method for screening neomycin analogs having anti-angiogenic activity. A preferred embodiment of the invention relates to using neomycin to treat subjects having such diseases. A dose of 20 ng neomycin/embryo or higher completely inhibited angiogenin-induced angiogenesis in the chorioallantoic membrane (CAM) assay. Neomycin inhibits angiogenin-induced angiogenesis mainly through inhibition of nuclear translocation of angiogenin.
CC 1-8
ST Miscellaneous Descriptors
neomycin analog angiogenesis inhibition antitumor
RN 11103-57-4 (Vitamin A)
9001-86-9 (Phospholipase C)
61912-98-9 (Insulin-like growth factor)
62229-50-9 (Epidermal growth factor)
65154-06-5 (Platelet activating factor)
97950-81-7 (Angiogenin (human))
106096-92-8 (Acidic fibroblast growth factor)
106096-93-9 (Basic fibroblast growth factor)
127464-60-2 (Vascular endothelial growth factor)
143011-72-7 (Granulocyte colony-stimulating factor)
66-86-4 (Neomycin C)
119-04-0 (Neomycin B)
1404-04-2 (Neomycin)
2037-48-1 (2-Deoxystreptamine)
3947-65-7 (Neomycin A)
7542-37-2 (Paromomycin)
11111-23-2 (Lividomycin)
25546-65-0 (Ribostamycin)
34051-04-2 (Nebramine)
35025-95-7 (Gentamine C1a)
50474-67-4 (Xylostasin)
51053-37-3 (Gentamine C1)

51053-38-4 (Gentamine C2)
84420-34-8 (Paromomycin)
50-18-0 (Cyclophosphamide)
50-35-1 (Thalidomide)
50-44-2 (6-Mercaptopurine)
50-76-0 (Dactinomycin)
50-91-9 (Floxuridine)
51-18-3 (Triethylenemelamine)
51-21-8 (Fluorouracil)
51-75-2 (Mechlorethamine)
51-79-6 (Urethane)
52-24-4 (Triethylenethiophosphoramide)
52-67-5 (D-Penicillamine)
53-19-0 (Mitotane)
53-79-2 (Puromycin)
54-25-1 (6-Azauridine)
54-91-1 (Pipobroman)
55-98-1 (Busulfan)
57-22-7 (Vincristine)
58-05-9 (Folinic acid)
58-19-5 (Dromostanolone)
59-05-2 (Methotrexate)
66-75-1 (Uracil mustard)
68-76-8 (Triaziquone)
69-33-0 (Tubercidin)
84-16-2 (Hexestrol)
89-38-3 (Pteropterin)
115-02-6 (Azaserine)
125-84-8 (Aminoglutethimide)
127-07-1 (Hydroxyurea)
147-94-4 (Cytarabine)
148-82-3 (Melphalan)
151-56-4Q (Aziridine, derivs.)
154-42-7 (Thioguanine)
154-93-8 (Carmustine)
157-03-9 (6-Diazo-5-oxo-L-norleucine)
302-22-7 (Chlormadinone acetate)
302-49-8 (Uredepa)
302-70-5 (Mechlorethamine oxide hydrochloride)
305-03-3 (Chlorambucil)
320-67-2 (Azacitidine)
362-07-2 (2-Methoxyestradiol)
459-86-9 (Mitoguazone)
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488-41-5 (Mitobronitol)
494-03-1 (Chlornaphazine)
520-85-4 (Medroxyprogesterone)
522-40-7 (Fosfestrol)
545-55-1 (Triethylenephosphoramide)
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566-48-3 (Formestane)
576-68-1 (Mannomustine)
595-33-5 (Megestrol acetate)
642-83-1 (Aceglatone)
645-05-6 (Altretamine)
801-52-5 (Porfiromycin)
865-21-4 (Vinblastine)
968-93-4 (Testolactone)
1402-44-4 (Actinomycin F1)
1403-28-7 (Carzinophilin)
1404-00-8 (Mitomycin)
1404-15-5 (Nogalamycin)
1508-45-8 (Podophyllinic acid 2-ethyl hydrazide)
1661-29-6 (Meturedepa)
1936-40-9 (Novembichin)
1954-28-5 (Etoglucid)
1980-45-6 (Benzodepa)
2363-58-8 (Epitiostanol)
2608-24-4 (Piposulfan)
2998-57-4 (Estramustine)
3094-09-5 (Doxifluridine)
3546-10-9 (Phenesterine)
3733-81-1 (Defosfamide)
3778-73-2 (Ifosfamide)
3819-34-9 (Phenamet)
3930-19-6 (Streptonigrin)
4291-63-8 (Cladribine)
4342-03-4 (Dacarbazine)
4533-39-5 (Nitracrine)
4803-27-4 (Anthramycin)
5581-52-2 (Thiamiprine)
5633-18-1 (Melengestrol)
8052-16-2 (Cactinomycin)
9014-02-2 (Zinostatin)
9015-68-3 (L-Asparaginase)
9042-14-2 (Dextran sulfate)
10318-26-0 (Mitolactol)
10540-29-1 (Tamoxifen)
11006-70-5 (Olivomycin)
11056-06-7 (Bleomycin)
13010-47-4 (Lomustine)
13311-84-7 (Flutamide)
13425-98-4 (Improsulfan)
13494-90-1 (Gallium nitrate)
13647-35-3 (Trilostane)
13665-88-8 (Mopidamol)
15663-27-1 (Cisplatin)
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17902-23-7 (Tegafur)
18378-89-7 (Plicamycin)
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37339-90-5 (Lentinan)
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41992-23-8 (Spirogermanium)
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50935-04-1 (Carubicin)
51264-14-3 (Amsacrine)
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53123-88-9 (Rapamycin)
53643-48-4 (Vindesine)
53714-56-0 (Leuprolide)
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54083-22-6 (Zorubicin)
54749-90-5 (Chlorozotocin)
55726-47-1 (Enocitabine)
56420-45-2 (Epirubicin)
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57982-77-1 (Buserelin)
57998-68-2 (Diaziquone)
58066-85-6 (Miltefosine)
58337-35-2 (Elliptinium acetate)
58957-92-9 (Idarubicin)
58970-76-6 (Ubenimex)
58994-96-0 (Ranimustine)
61163-28-8 (.beta.-1,3-Glucan sulfate)
61422-45-5 (Carmofur)
61825-94-3 (Oxaliplatin)
62435-42-1 (Perfosfamide)
63612-50-0 (Nilutamide)
64431-69-2 (Aclacinomycin S)
65271-80-9 (Mitoxanthrone)
65646-68-6 (Fenretinide)
65807-02-5 (Goserelin)
68247-85-8 (Peplomycin)
70052-12-9 (Eflornithine)
70563-58-5 (Herbimycin A)
71628-96-1 (Menogaril)
72496-41-4 (Pirarubicin)
72732-56-0 (Piritrexim)
74913-06-7 (Chromomycin)
78186-34-2 (Bisantrene)
80576-83-6 (Edatrexate)
82413-20-5 (Droloxifene)
84088-42-6 (Roquinimex)
85622-93-1 (Temozolomide)
86090-08-6 (Angiostatin)
87806-31-3 (Porfimer sodium)
89149-10-0 (15-Deoxyspergualin)
89778-26-7 (Toremifene)
90357-06-5 (Bicalutamide)
92118-27-9 (Fotemustine)
95058-81-4 (Gemcitabine)
98631-95-9 (Sobuzoxane)
99519-84-3 (CAI)
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103775-75-3 (Miboplatin)
110690-43-2 (Emitefur)
112809-51-5 (Letrozole)
112887-68-0 (Tomudex)
114977-28-5 (Docetaxel)
120511-73-1 (Anastrozole)
123948-87-8 (Topotecan)
126509-46-4 (Eponemycin)
126595-07-1 (Propagermanium)
129298-91-5 (AGM 1470)
130370-60-4 (Batimastat)
142298-75-7 (Ribonuclease inhibitor)
154039-60-8 (Marimastat)
187888-07-9 (Endostatin)
188417-67-6 (CM 101)

RN 100286-90-6; 196858-78-3; 197850-48-9; 197850-49-0; 250331-65-8; 250593-25-0

L8 ANSWER 38 OF 40 TOXCENTER COPYRIGHT 2003 ACS

AN 1999:40314 TOXCENTER
DN 99259140 PubMed ID: 10328588
TI New chemotherapy options for the treatment of malignant gliomas
AU Burton E; Prados M
CS University of California, San Francisco, Department of Neurosurgery, USA
NC CA09291 (NCI)
CA13525 (NCI)
SO CURRENT OPINION IN ONCOLOGY, 1999 May) 11 (3) 157-61. Ref: 24.
Journal Code: 9007265. ISSN: 1040-8746.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
FS MEDLINE
OS MEDLINE 1999259140
LA English
ED Entered STN: 20011116
Last Updated on STN: 20011116
AB Chemotherapy remains part of the treatment triad that includes surgery and radiation therapy for the management of malignant gliomas. In recent years there has been an increased understanding of the molecular pathways of malignant transformation. Based on this research, new drugs have been evaluated, with specific cellular targets in mind that can be modified or inhibited. Many of these agents are now being tested in phase I and II clinical trials and have shown some promising results. Clearly, not all patients with malignant gliomas respond equally to chemotherapy. Recent evidence suggests that certain molecular markers may predict chemosensitivity in some tumor types, particularly anaplastic oligodendroglioma. This article reviews recent trends in the use of chemotherapy and clinical trials of new therapies for adults with malignant gliomas.
CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
Adult
*Antineoplastic Agents: TU, therapeutic use
*Brain Neoplasms: DT, drug therapy
Brain Neoplasms: PP, physiopathology
Camptothecin: AA, analogs & derivatives
Camptothecin: TU, therapeutic use
Clinical Trials
Dacarbazine: AA, analogs & derivatives
Dacarbazine: TU, therapeutic use
Enzyme Inhibitors: TU, therapeutic use
*Glioma: DT, drug therapy
Glioma: PP, physiopathology
Neovascularization, Pathologic: PC, prevention & control
Oligodendroglioma: DT, drug therapy
Oligodendroglioma: GE, genetics
Protease Inhibitors: TU, therapeutic use
Signal Transduction: PH, physiology
Thalidomide: TU, therapeutic use
RN 100286-90-6 (irinotecan)
4342-03-4 (Dacarbazine)
50-35-1 (Thalidomide)
7689-03-4 (Camptothecin)
85622-93-1 (temozolomide)
CN 0 (Antineoplastic Agents); 0 (Enzyme Inhibitors); 0 (Protease Inhibitors)

L8 ANSWER 39 OF 40 USPATFULL
AN 2002:303979 USPATFULL
TI Use of neomycin for treating angiogenesis-related diseases
IN Hu, Guo-fu, Brookline, MA, United States
Vallee, Bert L., Boston, MA, United States
PA Endowment for Research in Human Biology, Inc., Boston, MA, United States (U.S. corporation)

PI US 6482802 B1 20021119
WO 9958126 19991118 <--
AI US 2000-700436 20001109 (9)
WO 1999-US10269 19990511
20001109 PCT 371 date
PRAI US 1998-84921P 19980511 (60)
DT Utility
FS GRANTED
REP US 2799620 Jul 1957 167/065.000 Waksman
US 5135919 Aug 1992 514/056.000 Folkman et al.
US 5135920 Aug 1992 514/059.000 Kanamaru et al.
US 5639725 Jun 1997 514/012.000 O'Reilly et al.
US 5698586 Dec 1997 514/475.000 Kishimoto et al.
US 5712291 Jan 1998 514/323.000 D'Amato
WO 9735567 Oct 1997
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Vallee BL, Riordan JF. Organogenesis and angiogenin. Cell Mol Life Sci. Oct. 1997;53(10):803-15.
EXNAM Primary Examiner: Raymond, Richard L.
LREP Pennie & Edmonds LLP
CLMN Number of Claims: 63
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 4 Drawing Page(s)
AB The present invention is directed to using neomycin or an analogue thereof as an therapeutic agent to treat angiogenesis-related diseases, which are characterized by excessive, undesired or inappropriate angiogenesis or proliferation of endothelial cells. The present invention is also directed to pharmaceutical compositions comprising (a) neomycin or an analogue and, optionally, (b) another anti-angiogenic agent or an anti-neoplastic agent. The present invention is further directed to a method for screening neomycin analogues having anti-angiogenic activity. A preferred embodiment of the invention relates to using neomycin to treat subjects having such diseases.

PARN This application is a 371 of PCT/US99/10209, filed May 16, 1999 and claims benefit under 35 U.S.C. .sctn.119 of U.S. Provisional Application No. 60/084,921 filed May 11, 1998.

SUMM 1. FIELD OF THE INVENTION

The present invention is directed to a method for treating subjects having an angiogenesis-related disease by administering neomycin or an analogue thereof. The present invention is also directed to a pharmaceutical composition comprising (a) neomycin or an analogue thereof, and, optionally, (b) another anti-angiogenic agent or an anti-cancer agent. The invention is further directed to a method for screening neomycin analogues having anti-angiogenic activity. In a preferred embodiment, neomycin is administered to subjects having angiogenesis-related diseases. In other embodiments, neomycin or an analogue thereof is administered with another anti-angiogenic agent. In

additional embodiments, neomycin or an analogue thereof is administered with an anti-neoplastic agent to treat subjects having an angiogenesis-related disease which is a cancer.

2. BACKGROUND OF THE INVENTION

2.1. Angiogensis

Angiogenesis is the complex process of blood vessel formation. The process involves both biochemical and cellular events, including (1) activation of endothelial cells (ECs) by an angiogenic stimulus; (2) degradation of the extracellular matrix, invasion of the activated ECs into the surrounding tissues, and migration toward the source of the angiogenic stimulus; (3) proliferation and differentiation of ECs to form new blood vessels (See, e.g., Folkman et al., 1991, J. Biol. Chem. 267:10931-10934).

The control of angiogenesis is a highly regulated process involving angiogenic stimulators and inhibitors. In healthy humans and animals, angiogenesis occurs under specific, restricted situations. For example, angiogenesis is normally observed in fetal and embryonal development, development and growth of normal tissues and organs, wound healing, and the formation of the corpus luteum, endometrium and placenta.

2.2. Angiogenesis-Related Diseases

The control of angiogenesis is altered in certain diseases. Many such diseases involve pathological angiogenesis (i.e., inappropriate, excessive or undesired blood vessel formation), which supports the disease state and, in many instances, contributes to the cellular and tissue damage associated with such diseases. Angiogenesis-related diseases (i.e., those involving pathological angiogenesis) are myriad and varied. They include, but are not limited to, various forms of tumors, chronic inflammatory diseases, and neovascularization diseases.

The formation and metastasis of tumors involve pathological angiogenesis. Like healthy tissues, tumors require blood vessels in order to provide nutrients and oxygen and remove cellular wastes. Thus, pathological angiogenesis is critical to the growth and expansion of tumors. Tumors in which angiogenesis is important include solid tumors as well as benign tumors such as acoustic neuroma, neurofibroma, trachoma and pyogenic granulomas.

Pathological angiogenesis also plays an important role in tumor metastasis. Pathological angiogenesis is important in two aspects. In one, the formation of blood vessels in tumors allows tumor cells to enter the blood stream and to circulate throughout the body. In the other, angiogenesis supports the formation and growth of new tumors seeded by tumor cells that have left the primary site.

Pathological angiogenesis is also associated with certain blood-borne tumors such as leukemias, and various acute or chronic neoplastic diseases of the bone marrow. It is believed that pathological angiogenesis plays a role in the bone marrow abnormalities that give rise to such leukemia-like tumors.

Pathological angiogenesis also plays a prominent role in various chronic inflammatory diseases such as inflammatory bowel diseases, psoriasis, sarcoidosis and rheumatoid arthritis. The chronic inflammation that occurs in such diseases depends on continuous formation of capillary sprouts in the diseased tissue to maintain an influx of inflammatory cells. The influx and presence of the inflammatory cells produce granulomas and thus, maintains the chronic inflammatory state.

For a general discussion of the role of angiogenesis in angiogenesis-related diseases see the following references: Moses et al., 1991, BioTechol. 9:630-633; Leek et al., 1994, J. Leuko. Biol. 56:423-435; and Beck et al., 1997, FASEB J. 11:365-373.

2.3. Angiogenic Factors and their Actions

Both normal and pathological angiogenesis apparently require action by one or more angiogenic factors. Many such factors have been identified. They include angiogenin (ANG), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), acidic fibroblast growth factor (aFGF), epidermal growth factor (EGF), tumor necrosis factor-alpha (TNF-.alpha.), tumor growth factor-alpha (TGF-.alpha.), and tumor growth factor-beta (TGF-.beta.).

There has not been a complete elucidation of the mechanism(s) by which angiogenic factors induce the various biochemical and cellular events of angiogenesis. However, much is known regarding the action of angiogenin in inducing angiogenesis, which may at least partially model the angiogenic action of other angiogenic factors.

Angiogenin was first isolated from tumor-conditioned culture medium as a result of a search for tumor angiogenic factors (Fett et al., 1985, Biochemistry 24:5480-5486). This search was based on the hypothesis that tumors will not grow beyond a minuscule size unless they are supplied with new blood vessels to provide nutrients and facilitate gas exchange (Folkman, J., 1971, N. Engl. J. Med. 285:1182-1186). Tumors elicit the formation of new blood vessels by secreting angiogenesis factors. Angiogenin has been shown to be a potent inducer of angiogenesis (Hu et al., 1998, in Human Cytokines, Handbook for Basic and Clinical Research, Vol. III, ed. Aggarwal, B. B. pp. 67-91, Blackwell Sciences, Inc., Maldan, Mass.). It induces the formation of new blood vessels in the chorioallantoic membrane (CAM) of chick embryos, and in the cornea and meniscus of the knee of rabbits (Fett et al., 1985, Biochemistry 24:5480-5486, King et al., 1991, J. Bone Joint Surg. 73-B: 587-590).

Angiogenin normally circulates in human plasma at a concentration of about 250 to 360 ng/ml (Blaser et al., 1993, Eur. J. Clin. Chem. Clin. Biochem. 31: 513-516, Shimoyama et al., 1996, Cancer Res. 56:2703-2706). Plasma angiogenin may promote wound healing when it becomes extravascular, e.g., through trauma. Angiogenin mRNA and protein are elevated in tissues and cells of patients with a variety of tumors (Chopra et al., 1995, Proc. Ann. Meet. Am. Assoc. Cancer Res. 36:A516; Li et al., 1994, J. Path. 172:171-175; and Moroianu et al., 1994, Proc. Natl. Acad Sci. USA 91:1677-1681).

Structure/function studies have shown that angiogenin has a weak but characteristic ribonucleolytic activity (Shapiro et al., 1986, Biochemistry 25:3527-35328). That activity appears to be essential for its angiogenic activity (Shapiro et al., 1989, Biochemistry 28:1726-17329). Compounds that inhibit angiogenin's ribonucleolytic activity also inhibits its angiogenic activity. Many such compounds have been identified or developed. They include the C-terminal peptides of angiogenin (Rybak et al., 1989, Biochem. Biophys. Res. Comm. 162:535-543), the ribonuclease inhibitor from human placenta (Lee et al., 1988, Biochemistry 27:8545-8553, Shapiro et al., 1987, Proc. Natl. Acad Sci. USA 84:2238-2241) and, more recently, a deoxynucleotide aptamer obtained by exponential enrichment.

Angiogenin apparently must interact with endothelial cells in order to induce angiogenesis. Several such interactions have been identified. Angiogenin binds to actin (Hu et al., 1991, Proc. Natl. Acad. Sci. USA 88:2227-2231, Hu et al., 1993, Proc. Natl. Acad Sci. USA 90:1217-1221) and to a 170 kDa putative receptor (Hu et al., 1997, Proc. Natl. Acad. Sci. USA 94:2204-2209) which are expressed on the surface of endothelial cells growing in dense and sparse culture, respectively. Binding of angiogenin to endothelial cells results in activation of phospholipase C (PLC) (Bicknell et al., 1988, Proc. Natl. Acad Sci. USA 85:5961-5965), endothelial cell migration and invasion (Hu et al., 1994 Proc. Natl. Acad Sci. USA 91:12096-12100), proliferation (Hu et al., 1997, Proc. Natl. Acad. Sci. USA 94:2204-2209), and differentiation (Jimi et al., 1995, Biochem. Biophys. Res. Comm. 211:476-483). A cell binding site on angiogenin has been identified. The site is essential for angiogenic activity and yet encompasses residues not involved in the ribonucleolytic activity (Hallahan et al., 1991, Proc. Natl. Acad Sci. USA 88:2222-2226; Hallahan et al., 1992, Biochemistry, 31:8022-8029). Interference with angiogenin's interaction with its target cells inhibit its angiogenic activity. For instance, both actin and an anti-actin antibody completely abolishes angiogenin-induced angiogenesis in the CAM of chick embryos (Hu et al., 1993, Proc. Natl. Acad Sci. USA 90:1217-1221). Moreover, administration of actin prevent the growth of transplanted human tumor cells in nude mice (Olson et al., 1995, Proc. Natl. Acad. Sci. USA 92:442-446).

Translocation of angiogenin to the nucleus is apparently essential for angiogenic activity. In the interaction with endothelial cells, angiogenin is internalized and translocated to the nucleus by a process that is lysosome and microtubule independent (Moroianu et al., 1994, Proc. Natl. Acad Sci. USA 91:1677-1681; Moroianu et al., 1994, Biochem. Biophys. Res. Comm. 203:1765-1772; Li et al., 1997, Biochem. Biophys. Res. Comm. 238:305-312). Mutated angiogenins that are incapable of nuclear translocation are also incapable of inducing angiogenesis in the CAM of chick embryos (Moroianu et al., 1994, Proc. Natl. Acad Sci. USA 91:1677-1681). Such mutated angiogenins, however, have full ribonucleolytic activity and can bind to endothelial cells.

While some other angiogenic factors do not necessarily have ribonucleolytic activity, they are internalized and translocated to the nucleus (See Savion et al., 1981, J. Biol. Chem. 256:1149-1154; Bouche et al., 1987, Proc. Natl. Acad. Sci. USA 84:6770-6774; Baldin et al., 1990, EMBO J. 9:1511-1517; Sano et al., 1990, J. Cell. Biol. 110:1417-1426; Quarto et al., 1991, J. Cell. Physiol. 147:311-318). Accordingly, it has been proposed that nuclear translocation is a general pathway for those angiogenic factors that is critical to their angiogenic activity (Moroianu et al., 1994, Proc. Natl. Acad. Sci. USA 91:1677-1681; Vallee et al., 1997, CMLS Cell. Molec. Life Sci. 53:803-815).

2.4. Anti-Angiogenic Agents

The centrality of angiogenesis in the myriad of angiogenesis-related diseases has motivated searches for anti-angiogenic agents (i.e., agents that suppress or inhibit pathological angiogenesis). Such searches typically involve examining the activity of candidate agents with in vivo angiogenesis assay systems. Two well established systems for carrying out such examinations are the CAM assay and the corneal neovascularization assay. These two systems examine an agent's effect on angiogenic factor-induced capillary formation in the chorioallantoic membrane of chick embryos and the cornea of laboratory animals, respectively (Gimbrone et al., 1974, J. Natl. Cancer Inst. 52:413-427).

Many anti-angiogenic agents have been isolated or developed. They include cartilage-derived factors (Moses et al., 1990, 248:1408-1410; Oikawa et al., 1990, Cancer Lett. 51:181-186); angiostatic steroids (Folkman et al., 1983, Science 221:719-725; Crum et al., 1985, Science 230:1375-1378; Oikawa et al., 1988, Cancer Lett. 43:85-92); and angiostatic vitamin D analogs (Oikawa et al., 1989, Cancer Lett. 48:157-162; Oikawa et al., 1990, Eur. J. Pharmacol. 178:247-50) angiostatin (O'Reilly et al., 1994, Cell 79:315-328), endostatin (O'Reilly et al., 1997, Cell 88:277-285), and verostatin (Pike et al. 1998, J. Exp. Med. 88:2309-2356).

Anti-angiogenic agents that inhibit the angiogenic activity of a specific angiogenic factor, angiogenin, have also been identified or developed. They include monoclonal antibody that binds angiogenin (Fett et al., 1994, Biochem. 33:5421-5427); human placental ribonuclease inhibitor (Shapiro et al., 1987, Proc. Natl. Acad. Sci. USA 84:2238-2241); actin (Hu et al., Proc. Natl. Acad. Sci. USA 90:1217-1221); and synthetic peptides corresponding to the C-terminal region of angiogenin (Ryback et al., 1989, Biochem. Biophy. Res. Comm. 162:535-543).

Anti-angiogenic agents of microbial origin also have been identified. Such agents include anthracycline (Npzaki et al., 1993, J. Antibiot. 46:569-579), 15-deoxyspergualin (Oikawa et al., 1991, J Antibiot. 44:1033-1035), D-penicillamine (Matsubara et al., 1989, J. Clin. Invest. 83:158-167), eponemycin (Oikawa et al., 1991, Biochem. Biophys. Res. Comm. 181:1070-1076), fumagillin (Ingber et al., 1990, Nature 348:555-557), herbimycin A (Oikawa et al., 1989, J. Antibiot. 42:1202-1204), and rapamycin (Akselband et al., 1991, Transplant Proc. 23:2833-2836).

Consistent with the idea that pathological angiogenesis underlies angiogenesis-related diseases, many anti-angiogenic agents have been demonstrated to have beneficial therapeutic activity against such diseases. Various types of tumors have been shown to be susceptible to treatments with anti-angiogenic agents. For example, several anti-angiogenin monoclonal antibodies exhibit significant antitumor activity in preventing or delaying the appearance of several different types of tumor xenografts in athymic mice (Olsen et al., 1994, Cancer Res. 54:4576-4579; Olson et al., 1995, Proc. Natl. Acad. Sci. USA 92:442-446). Actin, an angiogenin antagonist, has been shown to inhibit the establishment of various tumor xenografts in athymic mice (Olson et al., 1995, Proc. Natl. Acad. Sci. USA 92:442-446). Eponemycin inhibits the growth of B 16 melanomas (Sugawara et al., 1990, J Antibiot. 43:8-18). 22-oxa-1 .alpha.,25-dihydroxyvitamin D.sub.2, a potent angiogenesis inhibitor, has been shown to suppress the growth of autochthonous mammary tumors in rats (Oikawa et al., 1991, Anti-Cancer Drugs 2:475-480). AGM-1470, a synthetic anslog of fumagillin, has been shown to inhibit the growth of various types of transplanted tumors in mice (Ingber et al., 1990, Nature 348:555-557).

D-penicillamine, in the presence of copper, suppresses angiogenesis. It has been proposed that that activity accounts for the compound's efficacy in suppressing the inflammatory symptoms of rheumatoid synovitis, which involve pathological proliferation of small blood vessel in the synovium tissue (Matsubara et al., 1989, J. Clin. Invest. 83:158-167).

2.5. Neomycin

Neomycin is an aminoglycoside antibiotic derived from Streptomyces fradiae. It is bactericidal for many gram-negative and gram-positive organisms. It is in clinical use for oral treatment of enteral infections, to reduce microbe numbers in the colon prior to colon surgery, and orally or in enema form to reduce ammonia-producing bacteria in the treatment of hepatic encephalopathy. Absorption of neomycin from the intestinal tract is relatively poor. The usual oral dose is 4 to 8 Gm in divided doses per day. Neomycin is also administered intramuscularly, using a daily dose of 1 to 6 Gm. Damage to the kidney and the eighth nerve occurs in a significant number of patients when neomycin is given parenterally at a higher dose.

Citation or identification of any reference herein shall not be construed as an admission that such reference is available as prior art to the present invention.

3. SUMMARY OF THE INVENTION

The present invention provides a novel method for treating subjects having an angiogenesis-related disease. The method comprises administering to such subjects neomycin or an analogue thereof In a preferred embodiment, neomycin is administered to a subject having an angiogenesis-related disease. In other embodiments, neomycin or an analogue thereof is administered with other anti-angiogenesis agent(s) to such subjects. In additional embodiments, neomycin or an analogue thereof is administered with an anti-cancer agent to treat a subject having an angiogenesis-related disease which is a cancer.

Angiogenesis-related diseases involve excessive, inappropriate or undesired angiogenesis. Without intending to limit the present invention to any particular theory, it is believed that the disease state of angiogenesis-related diseases requires continuing action by one or more angiogenic factors, and such action requires nuclear translocation of the involved angiogenic factor(s). The present invention is based on the surprising discovery that neomycin and Analogues can inhibit nuclear translocation of angiogenic factors and have anti-angiogenic activity (i.e., inhibit angiogenic factor-induced angiogenesis).

The present invention is illustrated by way of examples that demonstrate the efficacy of neomycin in inhibiting the nuclear translocation of angiogenic factors, suppressing angiogenic factor-induced proliferation of endothelial cells, and inhibiting in vivo angiogenesis induced by certain angiogenic factors.

3.1. Definitions

In order to provide a clear and consistent understanding of the specification and claims, including the scope to be given to a term, the following definitions are given to various terms and abbreviations used herein.

aFGF acidic fibroblast growth factor
Analogue(s) the term "Analogue(s)" (capitalized) is used herein to mean analogue(s) of neomycin as defined in Section 5.1, infra.
anti-angiogenic the ability to inhibit angiogenesis, preferably angiogenic factor-induced angiogenesis
bFGF basic fibroblast growth factor
CAM chorioallantoic membrane
cancer a disease characterized by the formation of solid or blood borne tumors
EC endothelial cell
EGF epidermal growth factor
FBS fetal bovine serum
HE-SFM human endothelial serum-free medium
HUVE human umbilical vein endothelial
IP inositol phosphate
PBS phosphate-buffered saline
PLC phospholipase C
TGF-.alpha. tumor growth factor-alpha
TGF-.beta. tumor growth factor-beta
TNF-.alpha. tumor necrosis factor-alpha
VEGF vascular endothelial growth factor

DRWD 4. BRIEF DESCRIPTION OF THE FIGURES

FIG. 1. Neomycin inhibits nuclear translocation of .sup.125I-angiogenin in HUVE cells. HUVE cells, cultured at 50,000 cells per 35 mm dish, were treated with neomycin at the concentration indicated. .sup.125I-angiogenin was added to a final concentration of 1 .mu.g/ml and incubated at 37.degree. C. for 30 min. Nuclear fractions were isolated and radioactivities were determined. Data shown are relative percentage to the control and are from the mean of duplicate samples.

FIG. 2. Neomycin inhibits angiogenin-induced proliferation of HUVE cells. HUVE cells were cultured at a density of 4,000 cells per cm.sup.2 and were stimulated with 1 .mu.g/ml angiogenin in the absence or presence of neomycin at the concentration indicated at 37.degree. C. for 48 hr. Percentage increase of cell number stimulated by angiogenin in each neomycin concentration over the corresponding control was calculated from the mean of cell numbers of duplicate samples and was compared with that in the absence of neomycin, which was defined as 100% proliferative activity.

FIG. 3. Neomycin inhibits growth of PC-3 human prostate tumor cells in athymic mice. PC-3 human prostate tumor cells were harvested by trypsinization and viability was determined by trypan blue dye exclusion method. The cells, 1.times.10.sup.4, were mixed with 33 .mu.l of Matrigel and either control or neomycin at a dose of 20 mg/kg body weight. The preparation containing the cells, Matrigel and either control or neomycin was then diluted with PBS to a total volume of 100 .mu.l, which was injected subcutaneously at a site behind the left shoulder. Subsequent injection of PBS (dotted line) or neomycin (solid line) at a dose of 20 mg/kg body weight was administered subcutaneously 6 times per week for 20 days and 4 times per week for another 30 days.

FIG. 4. Neomycin inhibits growth of MDA-MB-435 human breast tumor cells in athymic mice. MDA-MB-435 human breast tumor cells were harvested by trypsinization and viability was determined by trypan blue dye exclusion method. A total of 1.times.10.sup.4 cells in 20 .mu.l was injected into the mammary fat pad of the mice. Daily treatment with PBS (dotted line) or neomycin (solid line) at a dose of 60 mg/kg body weight was administered intraperitoneally for 20 days followed by 4 times per week for another 42 days.

DETD 5. DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a method for treating or preventing angiogenesis-related diseases by administering neomycin or an Analogue. Angiogenesis-related diseases are associated with or supported by pathological angiogenesis (i.e., inappropriate, excessive or undesired formation of blood vessels), which apparently is induced by various angiogenic factors. The present invention is also directed to pharmaceutical compositions comprising neomycin or an Analogue and, optionally, another anti-angiogenic agent or an anti-cancer agent. The present invention is further directed to a method for screening neomycin analogues having anti-angiogenic activity.

According to the present invention, the aminoglycoside antibiotic neomycin and analogues thereof inhibit two apparently essential steps required for induction of angiogenesis by most, if not all, angiogenic factors: induction of proliferation of endothelial cells and nuclear translocation of the. angiogenic factor. More significantly, neomycin and analogues thereof inhibit pathological angiogenesis associated with many disease states.

In the examples provided infra, neomycin inhibited angiogenin-induced EC proliferation and angiogenin nuclear translocation with an IC.sub.50 of about 10 .mu.M and 50 .mu.M, respectively. Neomycin completely abolished angiogenin-induced angiogenesis in the chorioallantoic membrane (CAM) of chick embryos at a dosage of about 20 ng per embryo.

Neomycin also inhibited the actions of other angiogenic factors. It inhibited the nuclear translocation of angiogenic factors bFGF, aFGF, and EGF in endothelial cells. Proliferation of endothelial cells induced by these factors were inhibited by neomycin with an IC.sub.50 of about 100 .mu.M. Neomycin inhibited bFGF-, aFGF- and EGF-induced angiogenesis in the CAM of chick embryos at a dosage of about 200 ng per embryo.

Further, whereas neomycin inhibited VEGF-induced proliferation of endothelial cells, it did not significantly reduce the angiogenic activity of VEGF on the CAM of chick embryos at a dosage as high as 900 ng per embryo. Since VEGF is a pleiotropic angiogenic factor implicated in both normal and neoplastic angiogenesis, whereas other angiogenic factors may be more involved in pathological angiogenesis, these results suggest that neomycin may be used as an anti-angiogenic agent that selectively inhibits the pathological angiogenesis associated with many diseases, but not normal angiogenesis.

Additionally, neomycin caused no cytotoxicity in cultured human endothelial cells up to a concentration of about 200 .mu.M. Similarly, neomycin caused no necrosis or any other visible adverse effect on the chick embryo at the various dosage applied. Thus, therapeutic administration of neomycin or Analogue can be used to beneficially ameliorate the symptoms of angiogenesis-related diseases or suppress conditions that are required for developing or continuing such diseases.

5.1. Neomycin and Analogues

The present invention contemplates the use of neomycin or an analogue thereof in the method of the invention to treat or prevent an angiogenesis-related disease. As used herein, the term "neomycin" refers to the antibiotic complex composed of neomycins A, B and C (the complex is known by various common names such as Mycifradin, Myacyne, Fradiomycin, Neomin, Neolate, Neomas, Nivemycin, Pimavecort, Vonamycin Powder V). In a preferred embodiment, neomycin is used in the method of the invention to treat or prevent angiogenesis-related diseases.

As used herein, the term "neomycin analogue" refers to: (a) any individual component of the neomycin complex, i.e., neomycin A (also known as Neamine), or neomycin B (also known as Framycetin, Enterfram, Framygen, Soframycin, Actilin, and antibiotique EF 185), or neomycin C; or (b) a complex comprising neomycin A, neomycin B, or neomycin C; (c) an aminoglycoside having a structure substantially similar to that of neomycin A or B or C (hereinafter "structural analogue of neomycin"); or (d) a chemical or biological breakdown product of neomycin A or B or C, such as neobiosamine C, which is released upon hydrolysis of neomycin C; (e) a derivative of neomycin A or B or C, such as neomycin LP-B or neomycin LP-C; or (f) a naturally-occurring precursor to neomycin A or B or C.

As used herein, a structural analogue of neomycin is a substituted-2-deoxystreptamine (2-DOS) linked to two to four pentose or hexose sugars. Such structural analogues include, but are not limited to, the neomycin, paromomycin or lividomycin aminoglycoside family. Preferably, a structural analogue of neomycin has a glucosyl residue attached to the 4 position of the 2-DOS moiety, which glucosyl residue comprises an amino group at each of the 2 and 6 positions. Such preferred structural analogues of neomycin include, but are not limited to, nebramine, gentamine C.sub.1, gentamine C.sub.2, gentamine C.sub.1a, ribostamycin, xylostasin. For a discussion of the structure and biological activity of neomycin family of aminoglycosides and related aminoglycosides see Aminoglycoside Antibiotics, ed. Umezawa, Spriner, Berlin, 1982, and Rhinehart, K. L., The Neomycins and Related Antibiotics, Wiley & Sons, New York, 1961. As contemplated by the present invention, neomycin analogues may or may not have antimicrobial activity.

Neomycin analogues that may be used in the method of the invention preferably have structures that are substantially similar to that of neomycin B or C. As used herein, such substantially similar analogues are 4,5-disubstituted-2-deoxystreptamines comprising a 2-DOS and a 2,6-diamino-2-6-dideoxy-D-glucose (i.e., neosamine C) attached to the 4 position of 2-DOS.

Neomycin analogues that may be used in the method of the invention also can be selected based on the following biological criteria. In one embodiment, the neomycin analogue selected for use in the method of the invention (the "selected neomycin analogue") is one which inhibits (a) the nuclear translocation of an angiogenic factor, or (b) the ribonucleolytic activity of angiogenin. Neomycin analogues can be tested for such activity according to assays such as those described in Sections 6.1.1.4, 6.1.1.6 and 6.2.1, infra, or known in the art.

In yet another embodiment, the selected neomycin analogue is one which inhibits the activity of phospholipase C. Neomycin analogues can be tested for such activity according to known assays (see Somjen et al., 1997, J. Cell. Biochem. 65:53-66; Hildebrandt et al., 1997, Bri. J. Phar. 120:841-850).

In a preferred embodiment, the selected neomycin analogue is any of the following: neomycin A, neomycin B or neomycin C or a complex comprising neomycin A, neomycin B, or neomycin C.

In an additional preferred embodiment, the selected neomycin analogue is one which reduces or inhibits inflammatory angiogenesis. Neomycin analogues can be tested for such activity according to assays such as the murine airpouch granuloma model of chronic inflammation (see Kimura et al., 1985, J. Pharmacobio-Dyn. 8:393-400; Colville-Nash et al., 1995, J. Pharm. Exp. Ther. 274:1463-142; and International Publ. No. WO 07/35567).

In a further preferred embodiment, the selected neomycin analogue is one which inhibits angiogenic factor-induced proliferation of endothelial cells. Such activity can be determined using cell proliferation assays such as those that are described in Sections 6.1.1.5 and 6.3.1, infra, or known in the art.

In another preferred embodiment, the selected neomycin analogue is one which inhibits angiogenic factor-induced angiogenesis. In yet another preferred embodiment, the selected neomycin analogue is one which inhibits angiogenesis induced by an angiogenic factor other than VEGF. Neomycin analogues can be tested for their activity in inhibiting angiogenic factor-induced angiogenesis using the CAM assay, as described in Section 6.1.1.7, infra, the corneal neovascularization assay (Gimbrone et al., 1974, J. Natl. Cancer Inst. 52:413-427), or other similar assays known in the art.

According to the present invention, angiogenic factors include, but are not limited to, angiogenin (ANG), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), acidic fibroblast growth factor (aFGF), epidermal growth factor (EGF), tumor necrosis factor-alpha (TNF-.alpha.), tumor growth factor-alpha (TGF-.alpha.), and tumor growth factor-beta (TGF-.beta.), platelet-derived growth factor

(PDGF), platelet-derived endothelial cell growth fqactor (PD-ECGF), placental growth factor (PlGF), hepatocyte growth fctor (HGF), platelet activating factor (PAF), insulin-like growth factor (IGF), interleukin-8 (IL-8), and granulocyte-colony stimulating factor (GCSF).

5.1.1. Methods for Selecting Neomycin Analogues

The present invention provides methods for selecting neomycin analogues that can used in the therapeutic method of the invention. The contemplated selection methods include all of the assays referenced in Section 5.1, supra.

In a preferred embodiment, the selection method is based on an Analogue's activity for inhibiting nuclear translocation of an angiogenic factor. Such method may comprise (a) incubating endothelial cells with a neomycin analogue and a labeled-angiogenic factor; and (b) determining the amount of labeled-angiogenic factor present in the nuclei of such cells. Alternatively, the method may comprise (a) incubating endothelial cells in a growth medium with a neomycin analogue, (b) incubating the neomycin analogue-treated endothelial cells with a labeled-angiogenic factor; and (c) determining the amount of labeled-angiogenic factor present in the nuclei of the endothelial cells. The label attached to the angiogenic factor may be any known in the art including, but not limited to, a radioactive molecule or atom, a fluorescent molecule, and a phosphorescent molecule. In a specific embodiment, the method comprises (a) incubating a first culture of endothelial cells with the neomycin analogue and an angiogenic factor in a growth medium, and incubating a second culture of endothelial cells with the angiogenic factor in the growth medium lacking the neomycin analogue, wherein the angiogenic factor is labeled; (b) determining the amounts of angiogenic factor present in the nuclei of cells in the first and the second cultures; and (c) selecting for use in treating the angiogenesis-related disease, the neomycin analogue that inhibits nuclear translocation of the angiogenic factor in cells of the first culture by at least 10% of the amount of the angiogenic factor translocated to the nuclei of the cells in the second culture. In another embodiment, the method comprises (a) incubating a first culture of endothelial cells with the neomycin analogue in a growth medium, and incubating a second culture of endothelial cells in a growth medium lacking the neomycin analogue; (b) incubating the first and the second cultures with an angiogenic factor in the growth medium, wherein the angiogenic factor is labeled; (c) determining the amount of angiogenic factor present in the nuclei of cells in the first and the second cultures; and (d) selecting for use in treating the angiogenesis-related disease, the neomycin analogue that inhibits nuclear translocation of the angiogenic factor in the cells of the first culture by at least 10% of the amount of nuclear translocation of the angiogenic factor in the cells of the second culture. In preferred embodiments, a neomycin analogue is selected for use in the therapeutic method of the invention if it inhibits nuclear translocation of the angiogenic factor by at least 25% of the level of the angiogenic factor translocated to the nuclei of the control culture (i.e., cells that were not treated with the neomycin analogue). In a most preferred embodiment, the selected neomycin analogue inhibits nuclear translocation of the angiogenic factor by at least 50% of the level of the angiogenic factor translocated to the nuclei of the control culture.

In another preferred embodiment, the selection method is based on an Analogue's activity for inhibiting the proliferation of endothelial cells induced by an angiogenic factor. Such method may comprise (a) incubating endothelial cells in a neomycin analogue containing growth medium with or without an angiogenic factor; (b) determining the cell numbers of the cultures with or without the angiogenic factor; and (c) comparing the percentage decrease or increase in cell number in the culture treated with the angiogenic factor and the Analogue over that of the culture treated with just the Analogue with the percentage decrease or increase in cell number in a culture treated with the same concentration of angiogenic factor over that of a culture not treated with the angiogenic factor. In a specific embodiment, the method comprises (a) incubating a first culture of endothelial cells with the neomycin analogue and an angiogenic factor in a growth medium, incubating a second culture of endothelial cells with the neomycin analogue in the growth medium lacking the angiogenic factor, incubating a third culture of endothelial cells with the angiogenic factor in the growth medium lacking the neomycin analogue, incubating a fourth culture of endothelial cells in the growth medium lacking the neomycin analogue and the angiogenic factor; (b) determining the cell numbers of the first, the second, the third and the fourth cultures; and (c) selecting for use in treating the angiogenesis-related disease, the neomycin analogue that reduces the increase in the cell number in the second culture over the cell number in the first culture to less than about 75% of the increase in cell number of the third culture over the cell number of the fourth culture. In a preferred embodiment, a neomycin analogue is selected for use in the therapeutic method of the invention if it inhibits the proliferation of endothelial cells to less than 50% of the level of angiogenic factor-induced proliferation in the control cultures. In a most preferred embodiment, the selected neomycin analogue completely inhibits the proliferation of endothelial cells induced by the angiogenic factor.

The endothelial cells used in the above-described assays may be any known in the art, preferably HUVE. The growth medium used such assays may also be any known in the art, preferably, HE-SFM.

In a more preferred embodiment, the selection method is based on an Analogue's activity for inhibiting angiogenesis induced by an angiogenic factor. Such method may comprises the CAM assay as known in the art (see, e.g., Knighton et al., 1977, Br. J. Cancer 35:347-356; Fett et al., 1985, Biochemistry 24:5480-5486) or the corneal neovascularization assay as known in the art (see, e.g., Gimbrone et al., 1974, J. Natl. Cancer Inst. 52:413-427). The CAM assay may comprise: (a) applying an neomycin analogue to CAM of chick embryos treated with or without an angiogenic factor; (b) incubating the treated chick embryos; (b) determining the number of embryos having an angiogenic response (i.e., formation of blood vessels); and (d) comparing the percentage decrease or increase of angiogenic response in the embryos treated with the angiogenic factor and the analogue over the angiogenic response in the embryos treated with just the analogue, with the percentage decrease or increase in angiogenic response in embryos treated with the same concentration of angiogenic factor over that of embryos not treated with the angiogenic factor. In a specific embodiment, the CAM assay comprises (a) contacting the chorioallantoic membrane of a first group of chick embryos with the neomycin analogue and an angiogenic factor, contacting the chorioallantoic membrane of a second group of chick embryos with the neomycin analogue but not the angiogenic factor, contacting the chorioallantoic membrane of a third group of chick embryos with the angiogenic factor but not the neomycin analogue, and contacting the chorioallantoic membrane of a fourth group of chick embryos with a solution lacking the neomycin analogue and the antigenic factor; (b) incubating the first, the second, the third and the fourth groups of chick embryos; (c) determining the numbers of embryos having an angiogenic response in the first, the second, the third and the fourth groups of embryos; and (d) selecting for use in treating the angiogenesis-related disease, the neomycin analogue that reduces the increase in the number of embryos exhibiting an angiogenic response in the second group of embryos over the number of embryos exhibiting an angiogenic response in the first group of embryos to less than about 75% of the increase in the number of embryos exhibiting an angiogenic response in the third group of embryos over the number of embryos exhibiting an angiogenic response in the fourth group of embryos. In a more preferred embodiment, the selected neomycin analogue inhibits angiogenic factor-induced angiogenesis to less than 50% of the level of angiogenic factor-induced angiogenesis in the control groups of embryos (i.e., those contacted with or without the angiogenic factor only). In a more preferred embodiment, the selected neomycin analogue inhibits angiogenic factor-induced angiogenesis to less than 25% of the level of angiogenic factor-induced angiogenesis in the control groups of embryos.

5.2. Therapeutic Methods and Compositions

The present invention is directed to a method for treating a subject having an angiogenesis-related disease which comprises administering to the subject a therapeutic amount of neomycin or analogue thereof sufficient to (a) inhibit the pathological angiogenesis associated with the disease, or (b) ameliorate or eliminate any other pathological symptoms of the disease. As used herein, the term "inhibit" means suppress, arrest, prevent, reduce or retard, and the term "pathological angiogenesis" refers to the inappropriate, excessive or undesired formation of blood vessels that is associated with an angiogenesis-related disease or that supports continuation of the disease.

The subject treated by the methods of the invention is an animal, preferably a mammal, and more preferably a human. In one embodiment, the present invention is directed to treatment or prevention of angiogeneasis-related diseases of humans. In another embodiment, the present invention is directed to treatment or prevention of angiogenesis-related diseases of domestic animals, such as murine, rodent, feline or canine subjects, and farm animals, such as but not limited to bovine, equine and porcine subjects.

The present invention provides pharmaceutical compositions which comprise neomycin or an analogue thereof, as described in Section 5.1, supra,. Such compositions may optionally (i.e., additionally) comprise other therapeutic agents including, but not limited to, other anti-angiogenic agents and/or anti-neoplastic agents.

According to the invention, such other anti-angiogenic agents include, but are not limited to, thalidomide (D'Amato et al. 1994, Proc. Natl. Acad. Sci. USA 91:4082-4085; U.S. Pat. No. 5,712,291); angiostatic steroids such as 2-methoxyestradiol (D'Amato et al. 1994, Proc. Natl. Acad. Sci. USA 91:3964-3968; see also Folkman et al., 1983, Science 221:719-725; Crum et al., 1985, Science 230:1375-1378; Oikawa et al., 1988, Cancer Lett. 43:85-92); endostatin (O'Reilly et al., 1997, Cell 88:277-285); angiostatin (O'Reilly et al., 1994, Cell 79:315-328; U.S. Pat. No. 5,639,725); platelet factor-4 (Maione et al., 1990, Science 247:77-79); anti-angiogenic sulfated polysaccharides such as dextran sulfate and beta-1,3-glucan sulfate (U.S. Pat. No. 5,135,9200; cytokines such as interferon-alpha (Folkman 1996, Scientific American 275:150) and interleukin-12 (Folkman 1996, Scientific American 275:150); anti-angiogenic cartilage-derived inhibitors (Moses et al., 1990, Science 248:1408-1410; Oikawa et al., 1990, Cancer Lett. 51:181-186); angiostatic vitamin D analogs such as 22-oxa-1 .alpha.,25-dihydroxyvitamin D.sub.2 (Oikawa et al., 1989, Cancer Lett. 48:157-162; Oikawa et al., 1990, Eur. J. Pharmacol. 178:247-50); antibodies that bind angiogenin, such as monoclonal antibodies 26-2F and 36 U (Fett et al., 1994, Biochemistry 33:5421-5427; Olson et al., 1995, Proc. Natl. Acad. Sci. USA 92:442-446) and chimeric or humanized anti-angiogenin antibodies (Piccoli et al., 1998, Proc. Natl. Acad. Sci. USA 95:4579-4583); peptide that interferes with angiogenin interaction with its receptor, such as NH2-Val-Phe-Ser-Val-Arg-Val-Ser-Ile-Leu-Val-Phe-COOH (SEQ ID NO: 1), NH.sub.2-Leu-Leu-Phe-Leu-Pro-Leu-Gly-Val-Ser-Leu-Leu-Asp-Ser-COOH (SEQ ID NO: 2), NH.sub.2-Ala-Gln-Leu-Ala-Gly-Glu-Cys-Arg-Glu-Asn-Val-Cys-Met-Gly-Ile-Glu-Gly-Arg-COOH (SEQ ID NO: 3) and derivatives thereof (Gho et al., 1997, Cancer Res. 57:3733-3440; Gho et al., 1997, J. Biol. Chem. 272:24294-24299); human placental ribonuclease inhibitor (Shapiro et al., 1987, Proc. Natl. Acad. Sci. USA 84:2238-2241); actin and fragments thereof that interferes with angiogenin interaction with its receptor, such as NH.sub.2-Tyr-Ser-Val-Trp-Ile-Gly-Gly-Ser-Ile-Leu-Ala-Ser-Leu-Ser-Thr-Phe-Gln-Gln-Met-Trp-Ile-Ser-Lys-COOH (SEQ ID NO: 4) and derivatives thereof (Hu et al., Proc. Natl. Acad. Sci. USA 90:1217-1221); nucleotides that inhibit the ribonucleolytic activity of angiogenin, such as 5'-CGGACGAATGCTTTGATGTTGTGCTGGACCAGCGTTCATTCTCA-3'(SEQ ID NO: 5) and derivatives thereof; anthracycline; 15-deoxyspergualin; D-penicillamine; eponemycin; fumagillin and its derivatives such as AGM-1470 (Ingber et al., 1990, Nature 348:555-557; U.S. Pat. Nos. 5,135,919 and 5,698,586); herbimycin A; rapamycin; CAI (Folkman J., 1996, Sci. Amer. 275:150); CM101 (Folkman J., 1996, Sci. Amer. 275:150); and marimastat (Folkman J., 1996, Sci. Amer. 275:150).

The pharmaceutical compositions of the invention may optionally comprise one or more anti-neoplastic agents, which include, but are not limited to, alkaloids such as docetaxel, etoposide, irontecan, paclitaxel, teniposide, topotecan, vinblastine, vincristine, and vindesine; alkylating agents such as busulfan, improsulfan, piposulfan, aziridines, benzodepa, carboquone, meturedepa, uredepa, altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, chlorambucil, chlorophazine, cyclophosphamide, estramustine, ifosfamide, mechlorsthamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, perfosfamide, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, temozolomide; antibiotics and analogues such as aclacinomycinsa actinomycin F.sub.1, anthramycin, azaserine, bleomycins, cactinomycin, carubicin, carzinophilin, chromomycins, dactinomycin, daunorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, idarubicin, menogaril, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, pirarubicin, plicamycin, porfiromycin, puromycin, streptonigrin, streptozocin, tubercidin, zinostatin, zorubicin; antimetabolites such as denopterin, edatrexate, methotrexate, piritrexim, pteropterin, Tomudex.RTM., trimetrexate, cladribine, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carnofur, cytarabine, doxifluridine, emitefur, enocitabune, floxuridine, fluorouracil, gemcitabine, tegafur; L-Asparaginase; immunomodulators such as interferon-.alpha., interferon-.beta., interferon-.gamma., interleukin-2, lentinan, propagermanium, PSK, roquinimex, sizofican, ubenimex; platimum complexes such as carboplatin, cisplatin, miboplatin, oxaliplatin; aceglarone; amsacrine; bisantrene; defosfamide; demecolcine; diaziquone; eflornithine; elliptinium acetate; etoglucid; fenretinide; gallium nitrate; hydroxyurea; lonidamine; miltefosine; mitoguazone; mitoxantrone; mopidamol; nitracine; pentostain; phenamet; podophyllinic acid 2-ethyl-hydrazide; procabazine; razoxane; sobuzoxane; spirogermanium; tenuzonic acid; triaziquone; 2,2',2"trichlorotriethylamine; urethan; antineoplastic hormone or analogues such as calusterone, dromostanolone, epitiostanol, mepitiostane, testolacone, aminoglutethimide, mitotane, trilostane, bicalutamide, flutamide, nilutamide, droloxifene, tamoxifen, toremifene, aminoglutethimide, anastrozole, fadrozole, formestane, letrozole, fosfestrol, hexestrol, polyestradiol phosphate, buserelin, goserelin, leuprolide, triptorelin, chlormadinone acetate, medroxyprogesterone, megestrol acetate, melengestrol; porfimer sodium; batimastar; and folinic acid. For a description of these and other antineoplastic agents that may comprise the pharmaceutical composition of the invention see

The Merck Index, 12th ed. pp. THER 13-14. Compositions comprising an anti-neoplastic agent are particularly useful for treating angiogenesis-related diseases that are cancers (i.e., solid or blood-borne tumors).

According to the present invention, compositions of the invention can be administered by any of the routes used conventionally used for drug administration. Such routes include, but are not limited to, orally, topically, parenterally and by inhalation. Parenteral delivery may be intraperitoneal, intravenous, perioral, subcutaneous, intramuscular, intraarterial, etc.

Compositions of the invention may be administered in conventional dosage forms prepared by combining with standard pharmaceutically acceptable carriers according to procedures known in the art. Such combinations may involve procedures such as mixing, granulating, compressing and dissolving the appropriate ingredients.

The form and nature of the pharmaceutically acceptable carrier is controlled by the amounts the active ingredient with which it is combined, the route of the administration and other well-known variables. As used herein, the term "carrier" refers to diluents, excipients and the like for use in preparing admixtures of a pharmaceutical composition. The term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. Such pharmaceutically acceptable carriers or diluents and methods for preparing are well known in the art (see, e.g., Remington's Pharmaceutical Sciences, Meade Publishing Col., Easton, Pa., latest edition; the Handbook of Pharmaceutical Excipients, APhA publications, 1986).

Pharmaceutically acceptable carriers may be, for example, a liquid or solid. Liquid carriers include, but are not limited, to water, saline, buffered saline, dextrose solution, preferably such physiologically compatible buffers as Hank's or Ringer's solution, physiological saline, a mixture consisting of saline and glucose, and heparinized sodium-citrate-citric acid-dextrose solution and the like, preferably in sterile form. Exemplary solid carrier include agar, acacia, gelatin, lactose, magnesium stearate, pectin, talc and like.

Compositions of the invention can be administered orally. For such administrations, the pharmaceutical composition may be in liquid form, for example, solutions, syrups or suspensions, or may be presented as a drug product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats or oils); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). The pharmaceutical compositions may take the form of, for example, tablets, capsules or pellets prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinyl pyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well-known in the art.

For buccal administration, the compositions may take the form of tablets, troche or lozenge formulated in conventional manner.

Compositions, e.g., for oral or buccal administration, may be suitably formulated to give controlled release of the active compound. Such formulations may include one or more sustained-release agents known in the art, such as glyceryl mono-stearate, glyceryl distearate and wax.

Compositions of the invention may be applied topically. Such administrations includes applying the compositions externally to the epidermis, the mouth cavity, and the instillation into the eye, ear and nose, such that the neomycin or Analogue does not significantly enter the blood stream. This contrasts with systemic administration achieved by oral, intravenous, intraperitoneal and intramuscular delivery.

Compositions for use in topical administration include, e.g., liquid or gel preparations suitable for penetration through the skin such as creams, liniments, lotions, ointments or pastes, and drops suitable for delivery to the eye, ear or nose.

According to the invention, creams, drops, liniments, lotions, ointments and pastes are liquid or semi-solid compositions for external application. Such compositions may be prepared by mixing the active ingredient(s) in powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid with a greasy or non-greasy base. The base may comprise complex hydrocarbons such as glycerol, various forms of paraffin, beeswax; a mucilage; a mineral or edible oil or fatty acids; or a macrogel. Such compositions may additionally comprise suitable surface active agents such as surfactants, and suspending agents such as agar, vegetable gums, cellulose derivatives, and other ingredients such as preservatives, antioxidants, etc.

According to the invention, lotions and drops include those suitable for application to the eye or skin. Eye lotions and drops may comprise a sterile aqueous solution, oily solutions or suspensions maybe prepared by dissolving the active ingredient(s) in a suitable aqueous solution. Such solutions may optionally contain a suitable bactericide, fungicide, preservative, and surfactant. Lotions or liniments for applying to the skin may also comprise drying agents such as alcohol and/or a moisturizer such as glycerol, an oil or fatty acid.

Compositions of the invention also can be administered nasally or by inhalation. For nasal or inhalation administration, the compositions are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

Compositions of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophilic drugs.

Compositions of the invention comprise neomycin or Analogue, which may be in the form of a free base or acid, or a pharmaceutically acceptable salt thereof. Such salts are well known in the art. They include, but are not limited to, salts of inorganic and organic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, acetic acid, citric acid, fumaric acid, lactic acid, maleic acid, oxalic acid, phenylacetic acid, salicylic acid, succinic acid, and tartaric acid.

In preferred embodiments, compositions of the invention comprise an active ingredient (i.e., neomycin, Analogues, anti-angiogenic agents, and anti-neoplastic agents) that is a purified preparation.

Techniques and formulations for administering above-described compositions may be found in Remington's Pharmaceutical Sciences, Meade Publishing Col., Easton, Pa., latest edition.

5.3. Administration of Neomycin or Analogue

The present invention contemplates administration of pharmaceutical compositions comprising neomycin or analogue thereof to (a) inhibit the pathological angiogenesis associated with an angiogenesis-related disease, or (b) ameliorate or eliminate any other pathological symptoms of the disease. The dose of the neomycin or Analogue to be administered is a therapeutic amount effective to inhibit the formation or spread of inappropriate, undesired or excessive blood vessels at the disease site, e.g., as detected by such ability in vivo, or as extrapolated from in vitro assays (e.g., an assay that determines activity in inactivating or inhibiting the angiogenic factor-induced proliferation of endothelial cells) or from an animal model system such as the CAM assay or the corneal neovascularization assay. According to the invention, neomycin or Analogue may be administered in a single dose, or sustained administration, e.g., by intravenous (IV) drip or pump, or multiple doses.

Where the administration is in form of multiple doses, it should be at a frequency that is effective to inhibit the formation or spread of inappropriate, undesired or excessive blood vessels at the disease site, e.g., as detected by such ability in vivo, or as extrapolated from in vitro assays (e.g., an assay that determines activity in inactivating or inhibiting the angiogenic factor-induced proliferation of endothelial cells) or from an animal model system such as the CAM assay or the corneal neovascularization assay.

The present invention contemplates a daily dosage of neomycin or Analogue from about 0.5 .mu.g/kg body weight/day to about 0.1 gm/kg body weight/day when the composition of the invention is administered orally, and from about 0.5 .mu.g/kg body weight/day to about 0.06 gm/kg body weight/day when the composition is administered parenterally.

Where the subject being treated is human, in one embodiment of the present invention, neomycin is administered orally to the subject in divided doses totalling from about 4 Gm to about 8 Gm per day; in another embodiment, neomycin is administered intramuscularly to the subject using a daily dose of about 1 to about 6 Gm; in another embodiment, neomycin is administered parenterally to the subject using a dosage of 6 Gm or less.

The schedule of the neomycin or Analogue treatment should be at a periodicity that is sufficient to inhibit the formation or spread of inappropriate, undesired or excessive blood vessels at the disease site, and allows the subject to partially or completely recover from any undesirable side-effects caused or contributed to by the neomycin or Analogue treatment.

The duration of the neomycin or Analogue treatment should be for the length of time sufficient to inhibit the formation or spread of inappropriate, undesired or excessive blood vessels at the disease site, or preferably to cure the angiogenesis-related disease. The present invention contemplates a duration of treatment from one day up to several months.

The choice of the particular composition, form for administration, and effective dosages, as well as the frequency, schedule and duration of treatment will vary depending in part on the angiogenesis-related disease being treated.

5.4. Angiogensis-Related Diseases

The present invention provides method for treating or curing angiogenesis-related diseases, which involve excessive, inappropriate or undesired angiogenesis (i.e., pathological angiogenesis). Angiogenesis-related diseases may also involve excessive, inappropriate or undesired proliferation and/or migration of endothelial cells. Many diseases are associated with, or based on pathological angiogenesis or proliferation of endothelial cells. Angiogenesis-related diseases are myriad and varied. They include, but are not limited to, various forms of neovacularization or hypervascularization diseases, inflammatory diseases, arthritis and cancer.

As contemplated by the present invention, many solid and blood-borne tumors are angiogenesis-related diseases and are susceptible to treatment by the method of the invention. Solid tumors that may be treated by the method of the invention include, but are not limited to sarcomas and carcinomas, e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, and benign solid tumors such as acoustic neuroma, neurofibroma, trachoma and pyogenic granulomas.

Blood-borne tumors such as leukemias that are susceptible to treatment by the method of the invention include, but are not limited to, acute lymphocytic leukemia and acute myelocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia (chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia); and polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, and heavy chain disease.

Many corneal diseases involve pathological neovascularization, and hence are angiogenesis-related diseases and susceptible to treatment by the method of the invention. Such corneal neovascularization diseases include, but are not limited to, acne rosacea, atopic keratitis, bacterial ulcers, chemical bums, contact lens overwear, corneal graft rejection, diabetic retinopathy, epidemic keratoconjunctivitis, fungal ulcers, Herpes simplex infections, Herpes zoster infections, Kaposi sarcoma, lipid degeneration, marginal keratolysis, mycobacteria infections, Mooren ulcer, neovascular glaucoma and retrolental

fibroplasia, periphigoid radial keratotomy, phylectenulosis, polyarteritis, protozoan infections, pterygium keratitis sicca, retinopathy of prematurity, rheumatoid arthritis, sjogrens, scleritis, Steven's Johnson disease, superior limbic keratitis, syphilis, systemic lupus, Terrien's marginal degeneration, trauma, Vitamin A deficiency, and Wegeners sarcoidosis.

Similarly, many retinal/corneal diseases also involve pathological neovascularization, and thus are also angiogenesis-related diseases that are susceptible to treatment by the method of the invention. Such diseases include, but are not limited to, artery occlusion, Bechets disease, Bests disease, chronic retinal detachment, chronic uveitis/vitritis, carotid obstructive disease, diabetic retinopathy, Eales disease, hyperviscosity syndromes, infections causing a retinitis or choroiditis, Lyme's disease, macular degeneration, mycobacterial infections, optic pits, Pagets disease, pars planitis, post-laser complications, presumed ocular histoplasmosis, pseudoxanthoma elasticum, retinopathy of prematurity, sickle cell anemia, sarcoid, Stargarts disease, syphilis, systemic lupus erythematosis, toxoplasmosis, trauma, and vein occlusion. Other such diseases include, but are not limited to, diseases associated with rubeosis and diseases caused by the abnormal proliferation of fibrovascular or fibrous tissue including all forms of proliferative vitreoretinopathy, whether or not associated with diabetes.

Many chronic inflammatory diseases also involve pathological angiogenesis, and thus can be treated by the method of the present invention. Such diseases include, but are not limited to, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, psoriasis, rheumatoid arthritis, and sarcoidosis.

Other diseases that involve pathological angiogenesis include hemangiomas, Osler-Weber-Rendu disease, or hereditary hemorrhagic telangiectasia, and acquired immune deficiency syndrome.

Accordingly, subjects having angiogenesis-related diseases would also benefit from therapeutic treatment with the method of the invention.

The invention can be better understood by referring to the following examples, which are provided merely by way of exemplification and are not intended to limit the invention.

6. EXAMPLES

6.1. Neomycin Inhibits Angiogenin-Induced Angiogenesis

This set of experiments demonstrates that the aminoglycoside antibiotic neomycin, a known PLC inhibitor, is a potent inhibitor of both nuclear translocation of angiogenin, as well as angiogenin-induced cell proliferation and angiogenesis. The results indicate that neomycin is a new type of anti-angiogenic agent that may serve in the clinical treatment of angiogenesis-related diseases.

6.1.1. Materials and Methods

6.1.1.1. Materials

Human angiogenin (Met-1) was a recombinant product from an Escherichia coli expression system (Shapiro et al., 1988, Anal. Biochem. 175:450-461). Fertilized chicken eggs were from Spafas. Neomycin, amikacin, gentamicin, kanamycin, paromomycin, streptomycin, penicillin, amoxicillin, bacitracin, erythromycin, staurosporine, oxophenylarsine, yeast tRNA, and ribonuclease-free BSA were from Sigma Chemicals Co; U-73122 and U-73343 were from CalBiochem; genistein was from ICC; basic fibroblast growth factor (bFGF) was from Promega; human endothelial serum-free medium (HE-SFM) was from GIBCO/BRL-Life Technologies; fetal bovine serum (FBS) was from Hyclone; excellulose GF-5 desalting columns and Iodo-Beads iodination reagents were from Pierce; methyl-[.sup.3H]-thymidine (6.7 Ci/mmol, 1 Ci=37 Gbq) and Na.sup.125I (17.4 Ci/mg) were from Dupont/NEN.

6.1.1.2. Cell Culture

Human umbilical vein endothelial (HUVE) cells were purchased from Cell Systems Corp. (Kirkland, Wash.). The cells were cultured in HE-SFM supplemented with 10% FBS and 10 ng/ml bFGF at 37.degree. C. under 5% humidified CO.sub.2 and were split 1:3 for subculture. Cells between passages 5 and 12 inclusive were used for all experiments. Cell numbers were determined with a Coulter counter, and cell viability was measured by trypan blue dye exclusion assay.

6.1.1.3. Iodination of Angiogenin

.sup.125I-labeled angiogenin was prepared with the use of Iodo-Beads as described previously (Hu et al., 1997, Proc. Natl. Acad. Sci. USA 94:2204-2209). The specific activity of .sup.125I-angiogenin used in the experiments ranged from 1-2.times.10.sup.6 cpm/.mu.g.

6.1.1.4. Nuclear Translocation

HUVE cells were seeded at 5.times.10.sup.3 cells/cm.sup.2 in 35 mm dishes and cultured in HE-SFM supplemented with 20 ng/ml bFGF at 37.degree. C. under 5% humidified CO.sub.2 for 24 hr. The cells were washed three times with prewarmed (37.degree. C.) HE-SFM and incubated with .sup.125I-angiogenin (1 .mu.g/ml) at 37.degree. C. for 30 min. Two procedures were used to examine the effect of inhibitors on nuclear translocation. The first was to premix the inhibitors with 125I-angiogenin and adjust the sample volume to 10 .mu.l with HE-SFM before addition to the cells. The second was to pretreat the cells in HE-SFM with the inhibitors for 10 to 30 min before .sup.125I-angiogenin was added to the cells. After incubation, the dishes were cooled at 4.degree. C. for 10 min and the medium was removed. The cells were washed three times with cold phosphate-buffered saline (PBS), detached by scraping, and centrifuged at 800.times.g for 5 min. The cells were washed once with PBS and lysed by 0.5% Triton X-100 in PBS. The nuclear fraction was isolated by centrifugation at 1200.times.g for 5 min. Radioactivity was determined with a gamma counter.

6.1.1.5. Cell Proliferation

HUVE cells were seeded at 4.times.10.sup.3 cells/cm.sup.2 in attachment factor (Cell Systems Corp.)-coated 35 mm dishes in HE-SFM, and incubated with 1 .mu.g/ml angiogenin in the presence or absence of inhibitors at 37.degree. C. for 48 hr. Cell were detached by trypsinization and cell numbers were determined with a Coulter counter.

6.1.1.6. Ribonucleolytic Activity Assay

The effect of neomycin on the ribonucleolytic activity of angiogenin was examined with yeast tRNA as the substrate. Angiogenin, or its mixture with neomycin was added to an assay mixture containing 0.6 mg of yeast tRNA, 30 .mu.g of ribonuclease-free BSA, 30 mM HEPES, pH 6.8, and 30 mM NaCl in a final volume of 300 .mu.l. After incubation for 2 hr at 37.degree. C., 700 pl of 3.4% ice-cold perchloric acid was added, the mixture was vortexed, kept on ice for 10 mm and centrifuged at 15,000.times.g for 10 min at 4.degree. C. The absorbance of the supernatants was measured at 260 nm.

6.1.1.7. Angiogenesis Assay

Angiogenesis was measured on the CAM by the method of Knighton et al. (Knighton et al., 1977, Br. J. Cancer 35:347-356) essentially as described (Fett et al., 1985, Biochemistry 24:5480-5486). Fertilized chicken eggs were kept at 18.degree. C. for 2 days and then incubated in a humidified environment at 37.degree. C. for 3 days. Albumin was aspirated from the embryos and after 24 hours, a "window" was cut through the shell and covered with clear tape. The embryos were incubated for another 6 days at 37.degree. C. before an angiogenic factor and/or neomycin were applied. The angiogenic factor and/or neomycin each in about 5 .mu.l of H.sub.2O were applied to sterile, Thermanox 15-mm disks, dried under laminar flow, and applied to the CAM surface sample side down. After 48-68 hours at 37.degree. C., the growth of blood vessels was observed microscopically and recorded as either positive or negative. A positive response (i.e., an angiogenic response) has a typical "spokewheel" appearance.

6.1.2. Results

6.1.2.1. Neomycin Inhibits Nuclear Translocation of Angiogenin

Exogenously added angiogenin is rapidly taken up and translocated to the nucleus of proliferating endothelial cells (Moroianu et al., 1994, Proc. Natl. Acad Sci. USA 91:1677-1681). The mechanism of translocation is not yet known; but it seems to be energy and temperature dependent, suggesting the involvement of receptor-mediated endocytosis (Moroianu et al., 1994, Proc. Natl. Acad Sci. USA 91:1677-1681). Angiogenin also induces DNA synthesis and cell proliferation of sparsely cultured human endothelial cells (Hu et al., 1997, Proc. Natl. Acad. Sci. USA 94:2204-2209). Accordingly, the relationship of signal transduction and nuclear translocation was investigated by examining the effect of specific inhibitors of enzymes thought to be involved in the signal transduction process on the nuclear translocation of angiogenin in HUVE cells. As shown in Table 1, genistein and oxophenylarsine, inhibitors of tyrosine kinase and phosphotyrosine phosphatase (Mayer et al., 1995, J. Pharm. Exp. Therap. 274:427-436), respectively, have no effect on nuclear translocation of .sup.125I-angiogenin. Staurosporine, an inhibitor of protein kinase C, at its optimal concentration of 100 nM (Mayer et al., 1995, J. Pharm. Exp. Therap. 274:427-436), was only marginally inhibitory. However, 100 .mu.M neomycin, an aminoglycoside antibiotic and a PLC inhibitor (Somjen et al., 1997, J. Cell. Biochem. 65:53-66, Hildebrandt et al., 1997, Bri. J. Phar. 120:841-850), decreased the amount of .sup.125I-angiogenin accumulated in the cell nucleus after 30 min incubation by up to 60%. Another inhibitor of PLC, U-73122, also showed significant inhibition of nuclear translocation of .sup.125I-angiogenin (30% inhibition at 10 .mu.M), whereas, its inactive analogue, U-73343, had no effect. These data indicate that inhibitors of PLC inhibit nuclear translocation of angiogenin in HUVE cells, implying that PLC activity is required for translocation.

TABLE 1

Inhibition of Nuclear Translocation of Angiogenin
Nuclear .sup.125I-angiogenin
Inhibitors (cpm) % inhibition

Control 3090 .+-. 260 0
Genistein (100 .mu.M) 3300 .+-. 170 0
Oxophenylarsine (10 .mu.M) 3040 .+-. 70 0
Staurosporine (100 nM) 2710 .+-. 70 12
Neomycin (100 .mu.M) 1230 .+-. 60 60
U-73122 (10 .mu.M) 2140 .+-. 30 31
U-73343 (10 .mu.M) 2890 .+-. 100 6

HUVE cells, 50,000 per 35 mm dish, were treated with inhibitors at 37.degree. C. for 30 min .sup.125I-angiogenin was added to a final concentration of 1 .mu.g/ml and incubated at 37.degree. C. for 30 min.
Nuclear fractions were isolated and radioactivities determined.

Neomycin inhibits nuclear translocation of angiogenin in a dose-dependent manner (FIG. 1). Increasing concentration of neomycin progressively decrease the amount of nuclear accumulated .sup.125I-angiogenin from 3090.+-.260 cpm in the control to 420.+-.100 cpm in the presence of 500 .mu.M inhibitor. The inhibition is not linear. At 10 .mu.M, nuclear translocation is already inhibited by 42%. Increasing the concentration to 200 .mu.M only increases inhibition by another 23%. Nuclear translocation cannot be completely abolished by neomycin. At 500 .mu.M, the amount of .sup.125I-angiogenin that accumulates in the nucleus is 14% of that in the control.

6.1.2.2. Neomycin Inhibits Angiogenin-Induced Cell Proliferation

Exogenous angiogenin stimulates DNA synthesis and cell proliferation of sparsely cultured human endothelial cells (Hu et al., 1997, Proc. Natl. Acad. Sci. USA 94:2204-2209). Since neomycin inhibits nuclear translocation of angiogenin, the inhibitor's effect on angiogenin-induced cell proliferation was examined. When cells were cultured under the conditions described, essentially all were recovered after 48 hr in the absence of angiogenin and neomycin. In the presence of 1 .mu.g/ml angiogenin, cell number after 48 hr increased by 35%. Neomycin alone neither induced nor inhibited cell proliferation. However, it inhibited angiogenin-induced cell proliferation in a dose-dependent but non-linear manner. Thus, 5 .mu.M neomycin already inhibited the proliferative activity of angiogenin by 49% (FIG. 2). Increasing the neomycin concentration to 25 .mu.M inhibited angiogenin-induced cell proliferation by 69% and at 50 .mu.M, it was completely abolished.

6.1.2.3. Neomycin Inhibits Angiogenin-Induced Angiogensis

The ability of neomycin to inhibit angiogenin-induced angiogenesis was tested in the CAM assay. As shown in Table 2, neomycin itself at the concentration ranging from about 5 to about 50 .mu.M (20 to 200 ng in the 5 .mu.l volume applied) does not induce angiogenesis, nor does it cause necrosis or any other visible adverse effect on the chick embryo. Angiogenin alone at 10 ng induced a positive response in 55% of the chick embryos, consistent with previous results (Fett et al., 1985, Biochemistry 24:5480-5486). Neomycin at 4 ng decreased the number of angiogenic responses induced by 10 ng angiogenin from 55% to 40%, and at 20 ng decreased it to 20%, the same percentage obtained with water control. Thus, a dose of 20 ng neomycin/embryo or higher completely inhibits angiogenin-induced angiogenesis.

TABLE 2

Effect of Neomycin on the Activity of Angiogenin in the CAM Assay
Samples Total Embryos % Positive

Angiogenin (10 ng) 76 55
Neomycin (20 ng) 50 20
Neomycin (200 ng) 29 21
Angiogenin (10 ng) + 40 40
Neomycin (4 ng)
Angiogenin (10 ng) + 40 20
Neomycin (20 ng)

Angiogenin (10 ng) + 20 25
Neomycin (200 ng)
Water 128 20

Data were combined from multiple sets of experiments each using between 10 and 20 embryos.

6.1.2.4. Neomycin's Effect on the Ribonucleolytic Activity of Angiogenin

The effect of neomycin on the ribonucleolytic activity of angiogenin was examined with yeast tRNA as the substrate. The ribonucleolytic activity of angiogenin in the presence of 5 .mu.M, 10 .mu.M, and 50 .mu.M neomycin was 87%, 105% and 88% of that of the control. At higher concentrations, neomycin forms precipitates with tRNA. These results show that neomycin does not inhibit the cleavage of yeast tRNA by angiogenin even at a concentration of 50 .mu.M when the proliferative and angiogenic activities were already completely abolished. These data suggest that the inhibitory activity of neomycin on angiogenin-induced blood vessel formation is not attributable to its effect on the ribonucleolytic activity of angiogenin, but rather to its inhibition of nuclear translocation of angiogenin in endothelial cells and/or its inhibition of angiogenin-induced cell proliferation.

6.1.2.5. Effects of other Aminoglycoside Antibiotics on Angiogenin-Induced Cell Proliferation or Angiogenesis

Other members of aminoglycoside antibiotic family were also examined for their ability to inhibit angiogenin-induced proliferation of endothelial cells. None of the commonly used aminoglycosides-streptomycin, kanamycin, gentamicin and amikacin-inhibited angiogenin-induced cell proliferation (Table 3). Significantly, paromomycin, which differs from neomycin only at position 6 of the glucose ring, did not inhibit angiogenin-induced cell proliferation. Thus, a single substitution of --NH.sub.2 by --OH renders the aminoglycoside completely inactive as an anti-angiogenin agent. Data from CAM assay indicate that amikacin and streptomycin do not inhibit angiogenin-induced angiogenesis.

TABLE 3

Effects of Aminoglycoside Antibiotics on Angiogenin-induced Cell Proliferation

Aminoglycosides (100 .mu.M)	Angiogenin (1 .mu.g/ml) Cell number %*
None -	52,000 .+-. 100 120
+	62,500 .+-. 100
Neomycin -	52,700 .+-. 700 101
+	.sup. 53,400 .+-. 1,900
Amikacin -	51,700 .+-. 200 118
+	61,000 .+-. 400
Streptomycin -	.sup. 51,900 .+-. 1,300 115
+	59,900 .+-. 900
Kanamycin -	48,800 .+-. 400 121
+	58,900 .+-. 200
Gentamicin -	45,700 .+-. 500 121
+	55,700 .+-. 900
Paromomycin -	50,900 .+-. 500 116
+	58,900 .+-. 400

*percent of cell number in the presence of 1 .mu.g/ml angiogenin relative to the corresponding control.

6.1.3. Discussion

Neomycin, an aminoglycoside, is an antibiotic that inhibits translation by binding to the small subunit of prokaryotic ribosomes causing misreading of mRNA. Unlike its structurally related compound, geneticin (G-418), which is known to bind the 80S ribosomes and block protein synthesis in eukaryotic cells and is therefore useful as a selective marker for gene transfection in eukaryotic cells (Southern et al., 1982, J. Mol. Appl. Genet. 1:327-341), neomycin does not bind to eukaryotic ribosomes. Neomycin up to 200 .mu.M exhibited no cytotoxicity against HUVE cells. The cytotoxicity of other members of the aminoglycoside antibiotic family have also been examined. Such other aminoglycoside antibiotics, including amikacin, streptomycin, kanamycin, gentamicin and paromomycin, also exhibited no cytotoxicity against HUVE cells.

Among these aminoglycoside antibiotics, neomycin is the only one which shows inhibitory activity to angiogenin-induced cell proliferation. It is noteworthy that the structurally very similar aminoglycoside, paromomycin, has no inhibitory activity at all. Thus, the amino group on the carbon 6 of the glucose ring of neomycin apparently plays an important role in its inhibition of angiogenin-induced cell proliferation and angiogenesis.

Inhibition of nuclear translocation of angiogenin by neomycin is at least one of the reasons which lead to the inhibition of angiogenin-induced cell proliferation and angiogenesis. The concentrations required to inhibit nuclear translocation and cell proliferation by 50% are about 50 .mu.M and 10 .mu.M, respectively. Therefore, it is possible that some other functional aspects of neomycin, which remain to be investigated, may also contribute to its anti-angiogenesis activity.

Nuclear translocation of angiogenin in endothelial cells is thought to involve receptor-mediated endocytosis (Moroianu et al., 1994, Proc. Natl. Acad Sci. USA 91:1677-1681). However, binding of angiogenin to its surface receptor and the subsequent internalization do not seem to be inhibited by neomycin. Actually, neomycin induces a concomitant increase of cytosolic .sup.125I-angiogenin with the decrease of nuclear .sup.125I-angiogenin. If the PLC-inhibiting activity of neomycin is responsible for the inhibition of nuclear translocation of angiogenin, these results suggest that PLC activity is required for the steps subsequent to internalization in the nuclear translocation process. Since angiogenin activates PLC activity in endothelial cells (Bicknell et al., 1988, Proc. Natl. Acad Sci. USA 85:5961-5965) and PLC activity in turn is needed for nuclear translocation, the two cellular events may be interrelated and coordinate to function for the ultimate activity of angiogenin in endothelial cells. It is known that several cellular signal pathways activated by ligands binding to their receptors often crosstalk to obtain optimal cellular function (Jans, D. A., 1994, FASEB J. 8:841-847; Hopkins, C. R., 1994, Biochem. Pharma. 47:151-154).

Genistein, oxophenylarsine and staurosporine, which are inhibitors of tyrosine kinase, phosphotyrosine phosphatase and protein kinase C, respectively, do not inhibit nuclear translocation of angiogenin. It is unknown at present whether or not they inhibit angiogenin-induced proliferation and angiogenesis. If they do, the mechanisms would be different from that by which neomycin exerts its anti-angiogenesis effects.

The results disclosed here indicate that neomycin inhibits angiogenin-induced angiogenesis, mainly through its inhibition of nuclear translocation of angiogenin in endothelial cells. The data demonstrates that neomycin and its analogues are a new class of compounds having therapeutic use for treating angiogenesis-related diseases.

6.2. Neomycin Inhibits Nuclear Translocation of Other Angiogenic Factors

The following experiments demonstrate that neomycin inhibits nuclear translocation of angiogenic factors other than angiogenin.

6.2.1. Methods

Inhibition of nuclear translocation of angiogenic factors in HUVE cells was performed in the following manner. HUVE cells, passage 9 to 12, were cultured at 50,000 cells per 35 mm dish in HE-SFM supplemented with 20 ng/ml bFGF at 37.degree. C. for 24 hr. The cells were washed 3 times with prewarmed HE-SFM and treated with neomycin at various concentrations at 37.degree. C. for 10 min. .sup.125I-bFGF, .sup.125I-aFGF or .sup.125-EGF, 50 ng/ml, was added and incubated at 37.degree. C. for 30 min. At the end of incubation, the cells were cooled at 4.degree. C. for 10 min and washed 3 times with cold PBS (4.degree. C.), detached by scraping and centrifuged at 800.times.g for 5 min. The cell pellet was washed once with PBS and lysed with 0.5% triton X-100 in PBS. Nuclear fraction was isolated by centrifugation at 1200.times.g for 5 min. Radioactivity in the nuclear fraction was determined with a gamma counter.

6.2.2. Results

As shown in Table 4, neomycin inhibits nuclear translocation of bFGF, aFGF and EGF in HUVE cells in a dose- dependent manner. Neomycin's activity in inhibiting nuclear translocation of these three angiogenic factors in HUVE cells is not as strong as its activity against the translocation of angiogenin (see Section 6.1.2.1, supra). At 10 .mu.M, neomycin achieved 42% inhibition of the nuclear translocation of angiogenin, but only 13% and 15% inhibition of translocation of bFGF and aFGF, respectively. Nuclear translocation of EGF was not inhibited by neomycin until the latter's concentration exceeded 100 .mu.M. However, since nuclear translocation of angiogenic proteins in endothelial cells is absolutely required for angiogenesis to occur, these lesser inhibitory activities are still sufficient in suppressing angiogenesis induced by these angiogenic factors (see Section 6.4, infra).

TABLE 4

Neomycin Inhibits Nuclear Translocation of FGFs and EGF

Neomycin (.mu.M)	bFGF Counts (cpm)	% Inhib.	aFGF Counts (cpm)	% Inhib.	EGF Counts (cpm)	% Inhib.
0	18300 .+-. 200	--	7800 .+-. 100	--	140 .+-. 20	--
10	15900 .+-. 100	13	6600 .+-. 100	15	140 .+-. 20	0
50	14300 .+-. 100	22	5800 .+-. 100	26	140 .+-. 20	0
100	13500 .+-. 300	26	5300 .+-. 100	32	130 .+-. 30	7
150	12400 .+-. 200	32	4800 .+-. 100	38	120 .+-. 10	14
200	10900 .+-. 100	40	4500 .+-. 200	43	100 .+-. 20	29

6.3. Neomycin Inhibits Cell Proliferation Induced By Other Angiogenic Factors

These experiments demonstrate that neomycin inhibits cell proliferation induced by angiogenic factors other than angiogenin.

6.3. 1. Methods

Effect of neomycin on cell proliferation induced by angiogenic factors was performed in the following manner. HUVE cells, passage 8, were plated on attachment factor-coated 35 mm dish in HE-SFM at a density of 3000 cells/cm.sup.2. bFGF (10 ng/ml), aFGF (10 ng/ml), EGF (5 ng/ml) or VEGF (5 ng/ml) was added to the cells in the absence or presence of neomycin at different concentration immediately after the cells were seeded. The cells were incubated at 37.degree. C. under humidified air containing 5% CO.sub.2 for 48 hrs. At the end of the incubation, the cells were washed once with PBS and detached by trypsinization. Cell numbers were determined with a Coulter counter.

6.3.2. Results

As shown in Table 5, proliferation of HUVE cells induced by bFGF, aFGF and EGF was inhibited by neomycin in a dose-dependent manner. Thus, the proliferative activity of bFGF, aFGF and EGF was inhabited by 100 .mu.M neomycin by 41%, 50% and 59%, respectively. As shown in Section 6.1.2.2., supra, neomycin inhibits angiogenin-induced proliferation of HUVE cells with an IC.sub.50 value of <10 ,.mu.M. It appears that neomycin is a more potent and specific inhibitor for angiogenin than for the other angiogenic factors. VEGF is an angiogenic factor which has not been reported to undergo nuclear translocation in endothelial cells. Neomycin only has a small effect on VEGF-induced cell proliferation. Marginal inhibition (20%) was observed at 50 .mu.M of neomycin. At 50 .mu.M of neomycin, angiogenin-induced cell proliferation was already completely abolished. It is noteworthy that neomycin is not an effective inhibitor of cell proliferation induced by other angiogenic factors that have been tested. These results provides further evidence to support the hypothesis that neomycin inhibits angiogenesis, especially angiogenin-induced angiogenesis, via its inhibition of nuclear translocation of the angiogenic factors in endothelial cells.

TABLE 5

Inhibition of Cell Proliferation by Neomycin

Neomycin (.mu.M)	Control Cell No.	Inhib. %	bFGF Cell No.	Inhib. %	aFGF Cell No.	Inhib. %	VEGF Cell No.	Inhib. %
0	31400 .+-. 400		59600 .+-. 2600	--	73900 .+-. 2500	--	5300 .+-. 300	--
	45100 .+-. 200	--						
25	29800 .+-. 300	51	500 .+-. 700	19	60000 .+-. 400	25	46700 .+-. 600	17
	41000 .+-. 300	14						
50	28800 .+-. 1000		45900 .+-. 1200	34	51300 .+-. 400	42	41700 .+-. 600	35
	38900 .+-. 1300	20						
100	27900 .+-. 500	42	600 .+-. 200	41	46700 .+-. 800	50	35700 .+-. 1100	59
	36400 .+-. 400	22						
150	27400 .+-. 200	39	900 .+-. 125	49	41000 .+-. 1000	63	32800 .+-. 200	71
	35000 .+-. 200	36						
200	26300 .+-. 400	34	600 .+-. 400	64	37500 .+-. 200	68	26000 .+-. 900	100
	33800 .+-. 200	34						

6.4. Neomycin Inhibits Angiogenesis Induced By Other Angiogenic Factors

These experiments demonstrate that neomycin inhibits angiogenesis induced by other angiogenic factors.

6.4. 1. Methods

The ability of neomycin to inhibit bFGF-, CFGF-, EGF-, and VEGF-induced angiogenesis was tested in the CAM assay in a similar manner as described for angiogenin in Section 6.1.1.7, above.

6.4.2. Results

As shown in Table 6, aFGF, bFGF, and EGF, at 10 ng per egg, induced angiogenesis in 73, 78, and 69% of the eggs, respectively. The percentages of positive eggs induced by the same concentration of these three angiogenic factors in the presence of 20 ng neomycin were 36, 45, and 60%, respectively, representing an inhibition of their angiogenic activity by 71, 58, and 19%, respectively. In the presence of 200 ng neomycin, the percentage of positive eggs were 32, 34, and 30%, not significantly different from that of the water control (21%) tested simultaneously. Neomycin did not significantly inhibit the angiogenic activity of VEGF. In the absence or presence of 200 ng and 1 .mu.g neomycin, 10 ng of VEGF induced angiogenesis in 63, 58, and 52% of the eggs. Neomycin abolishes the angiogenic activity of angiogenin (10 ng) at a dose as low as 20 ng per egg (Section 6.1.2.3, above). Thus, neomycin inhibits angiogenesis induced by angiogenin, aFGF, bFGF and EGF, but not that stimulated by VEGF.

TABLE 6

Effect of neomycin on aFGF-, bFGF-, EGF- and VEGF-induced angiogenesis in CAM assay.

Neomycin Sample (ng)	Total eggs	Positive eggs	% Positive Inhibition.sup.a
aFGF (10 ng)	0	49	36 73 --
"	20	14	5 36 71
"	200	47	16 34 75
bFGF (10 ng)	0	37	29 78 --
"	20	33	15 45 58
"	200	38	12 32 81
EGF (10 ng)	0	26	18 69 --
"	20	15	9 60 19
"	200	30	9 30 81
VEGF (10 ng)	0	27	17 63 --
"	200	24	14 58 10
"	1000	27	14 52 24
water.sup.b	0	212	45 21 --
	20	50	10 20 --
	200	29	6 21 --
	1000	13	3 23 --

Angiogenesis was measured on the chorioallantoic membrane as described above in Section 6.1.1.7. Growth of blood vessels was observed microscopically and recorded as either positive or negative after 48 hr of incubation. Data were combined from multiple sets of experiments each using between 10 and 20 eggs.

The angiogenic activity of VEGF in the chick CAM was not significantly inhibited by neomycin. The level of angiogenic response induced by 10 ng VEGF in the presence of 200 ng and 1 .mu.g neomycin per embryo was 58% and 52%, respectively, not much different from that in the absence of neomycin (63%). These data are in agreement with the results obtained in the proliferation assay where neomycin does not significantly inhibit VEGF-induced proliferation of HUVE cells.

VEGF is a pleiotropic angiogenic factor implicated in both developmental neovascularization and neoplastic angiogenesis, whereas the other angiogenic factors may be only related to disease status. Therefore, the fact that neomycin does not inhibit the angiogenic activity of VEGF may, on the one hand, reflect the finding that VEGF does not undergo nuclear translocation. On the other hand, it implies that neomycin may be a selective inhibitor of angiogenesis involved only in pathological conditions but not in the neovascularization under physiological circumstance. This is significant to the use of neomycin and its analogues as therapeutic agents for use in clinical treatment of angiogenesis-dependent disease. It indicates that the use of neomycin as an anti-angiogenic agent is specific and would not cause developmental abnormality. Neomycin, at 250 .mu.M (1 .mu.g in the 5 .mu.l volume applied per embryo), did not cause necrosis or any other visible adverse effects on the chick embryo.

6.5. Other Aminoglycosides Do Not Inhibit FGF-Induced Cell Proliferations

These experiments demonstrate that other aminoglycoside antibiotics do not inhibit bFGF-induced proliferation of HUVE cells.

6.5. 1. Methods

The ability of the other members of the aminoglycoside antibiotic family to inhibit bFGF-induced proliferation of HUVE cells was examined in a similar manner as for angiogenin as described in Section 6.1.1.5, above. HUVE cells, passage 9, were seeded on attachment-factor coated dishes at 50,000 cells per 35 mm dish in HE-SFM. Aminoglycoside antibiotics were added and the cells were incubated with or without ng/ml bFGF at 37.degree. C. for 48 hr.

6.5.2. Results

As shown in Table 7, 100 .mu.M neomycin inhibited bFGF-induced proliferation of HUVE cells by 71%. By contrast, no other members of the aminoglycoside antibiotic family tested, including streptomycin, kanamycin, gentamicin and amikacin, exhibited any significant inhibitory effect on cell proliferation induced by bFGF. These results are very similar to that obtained with angiogenin-induced cell proliferation presented in Section 6.1.2.5, supra. These data indicate that the anti-angiogenic and anti-bacterial activity of neomycin may depend on the different properties of the molecule and can be separated. It is known that the anti-bacterial function of neomycin and the other aminoglycoside antibodies is the result of binding to the 16S rRNA and inhibition of initiation of protein synthesis. The anti-angiogenic activity of neomycin may derive from its inhibition of PLC via binding to PIP.sub.2, and the subsequent inhibition of nuclear translocation of angiogenic proteins. The lack of effect of other aminoglycoside antibiotics on the proliferative activity of angiogenin and bFGF further indicate that neomycin is a specific and selective inhibitor of angiogenesis.

TABLE 7

Effect of Aminoglycoside Antibiotics on bFGF-induced Cell Proliferation

Aminoglycoside (100 .mu.M)	bFGF (10 ng/ml) Cell % Control	Numbers	Inhibition
Control	61300 .+-. 500	99000 .+-. 1000	--
Neomycin	58000 .+-. 1500	68400 .+-. 800	71
Streptomycin	62300 .+-. 600	104200 .+-. 400	0
Kanamycin	62600 .+-. 1100	98000 .+-. 2500	8
Gentamicin	61800 .+-. 1200	98400 .+-. 1900	5
Amikacin	63000 .+-. 900	97600 .+-. 1300	11

6.6. Neomycin Inhibits Growth of PC-3 Human Prostate Tumor Cells in Athymic Mice

These experiments established that neomycin inhibits the establishment and growth of PC-3 human prostate tumor cells inoculated in athymic mice.

6.6.1. Methods

The subcutaneous tumor model in athymic mice has been used extensively to show that angiogenin antagonists such as monoclonal antibodies, its binding protein and antisense DNA, prevent the establishment of human tumor cells in mice (Olson et al., 1998, Proc. Am. Assoc. Cancer Res. 39:665A; Olson et al., 1994, Cancer Res. 54:4576-4579; Olson et al., 1995, Proc. Natl. Acad. Sci. USA 92:442-446. Olson KA et al., 1996, Proc. Am. Assoc. Cancer Res. 37:395A); none of these references, however, relate in any way to neomycin. As described below, this model is useful to examine the capacity of neomycin to delay or to prevent the establishment of PC-3 human prostate tumor cells in athymic mice.

Outbred athymic mice (6 mice per group) were injected subcutaneously with a mixture of 100 .mu.l containing 1.times.10.sup.4 PC-3 cells, 33 .mu.l of basement membrane components (Matrigel), and either PBS control or neomycin at a dose of 20 mg/kg body weight. The mice received subcutaneous injections proximal to the site of the original cell inoculation of PBS control or neomycin diluted in PBS at a dose of 20 mg/kg body weight 6 times per week for 20 days, followed by injection 4 times per week for another 30 days. Mice were examined daily by palpation for the first sign of tumor appearance at which time tumor size was estimated twice weekly by caliper measurements (longest perpendicular length and width).

6.6.2. Results

As shown in FIG. 3, treatment with neomycin prevented the appearance of PC-3 tumors in 50% of the mice. By day 18, 2 of 6 mice in the control group receiving PBS developed a tumor, whereas, all of the mice in the neomycin-treated group remained tumor-free. As of day 42, only 50% of the neomycin-treated as opposed to 100% of the animals in the control group had developed tumors. The dose (20 mg/kg body weight) used in this experiment was based on the usual intramuscular dose for human use (Wintrobe et al., 1971, Harrison's Principles of Internal Medicine, 6th ed., p749). There was no evidence of toxic side effects. No changes were observed between the control and neomycin-treated mice with respect to general activity, body weight, and food and fluid intake.

PC-3 cells are the most aggressive tumor cell line and are the least responsive one among the tumor cells so far tested for anti-angiogenin therapy. Thus, because neomycin is shown herein to be effective against PC-3 cells, it is expected to be more effective toward other tumor cells that are less aggressive than PC-3 cells.

6.7. Neomycin Inhibits Establishment and Growth of MDA-MB-435 Human Breast Tumor Cells in Athymic Mice

Theses experiments established that neomycin inhibits the establishment and growth of MDA-MB-435 human breast tumor cells inoculated in athymic mice.

6.7.1. Methods

An orthotopic model was chosen to evaluate the efficacy of neomycin in preventing the growth of human breast cancer cells. MDA-MA-435 human breast tumor cells, which are estrogen receptor negative, were injected directly into the mammary fat pad of athymic mice. Age-matched athymic female mice were assigned to treatment groups of 8 mice each and anesthetized with ketamine (212 mg/kg body weight) and xylazine (21.2 mg/kg body weight) given intraperitoneally and allowed to stabilize under anesthesia for 15 min. A heating pad was used to maintain their body temperature throughout the procedure to minimize stress. Betadine followed by 70% alcohol was swabbed onto the skin of the left lateral thorax. An incision of 6 mm in length was made through the skin in the area of the left lateral thorax behind the left front leg and the mammary fat pad was exposed by using gentle pressure with two fingers to separate the skin at the incision site. MDA-MB-435 human breast tumor cells were harvested by trypsinization, washed in HBSS, counted using trypan blue exclusion to determine cell viability, and 10,000 cells in a total volume of 20 .mu.l were injected into the fat pad using a 27 gauge needle. The incision was closed with 2 drops of Vetbond veterinarian tissue adhesive and the mouse was allowed to recover on the heating pad before returning to its cage. Treatment with neomycin or with control (PBS) started on day 1 and was given intraperitoneally daily for 20 days followed by injection 4 times per week for 42 days. A dosage of 60 mg neomycin per kg body weight was used in this experiment. Mice were examined daily for tumor growth by gentle palpation of the lateral left thorax in the general area of the injection.

6.7.2. Results

As shown in FIG. 4, intraperitoneal treatment with neomycin at 60 mg/kg body weight completely inhibited the establishment of MDA-MB-435 human breast tumors in athymic mice. By day 56, all the mice in the control group (8 mice) receiving only PBS developed tumors, whereas, in the neomycin-treated group, none of the mice had tumors. There was no sign of toxic side effects at this neomycin dosage (60 mg/kg body weight) when administered intraperitoneally for 62 days.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

GENERAL INFORMATION:
NUMBER OF SEQ ID NOs: 5
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 1
LENGTH: 11
TYPE: PRT
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: deduced from antisense RNA corresponding to the receptor-binding stie of angiogenin in 5'->3' direction
SEQUENCE: 1
Val Phe Ser Val Arg Val Ser Ile Leu Val Phe
1 5 10
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 2
LENGTH: 13
TYPE: PRT
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: deduced from antisense RNA corresponding to the receptor-binding stie of angiogenin in 3'->5' direction
SEQUENCE: 2
Leu Leu Phe Leu Pro Leu Gly Val Ser Leu Leu Asp Ser
1 5 10

SEQUENCE CHARACTERISTICS:
SEQ ID NO: 3
LENGTH: 18
TYPE: PRT
ORGANISM: Homo Sapiens
SEQUENCE: 3
Ala Gln Leu Ala Gly Glu Cys Arg Glu Asn Val Cys Met Gly Ile Glu
1 5 10 15
Gly Arg
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 4
LENGTH: 23
TYPE: PRT
ORGANISM: Homo Sapiens
SEQUENCE: 4
Tyr Ser Val Trp Ile Gly Gly Ser Ile Leu Ala Ser Leu Ser Thr Phe
1 5 10 15
Gln Gln Met Trp Ile Ser Lys
20
SEQUENCE CHARACTERISTICS:
SEQ ID NO: 5
LENGTH: 44
TYPE: DNA
ORGANISM: Homo Sapiens
SEQUENCE: 5
cggacgaatg ctttgatgtt gtgctggacc agcgttcatt ctca 44

CLM What is claimed is:

1. A method of inhibiting pathological angiogenesis or proliferation of endothelial cells in a subject, which method comprises administering to the subject an amount of neomycin or an analogue thereof sufficient to inhibit pathological angiogenesis or proliferation of endothelial cells.

2. The method according to claim 1, wherein the neomycin analogue is (a) neomycin A, neomycin B, or neomycin C; (b) a complex comprising neomycin A, neomycin B, or neomycin C; (c) an aminoglycoside having a structure substantially similar to that of neomycin A, neomycin B or neomycin C; (d) a chemical or biological breakdown product of neomycin A, neomycin B or neomycin C; (e) a derivative of neomycin A, neomycin B or neomycin C; or (f) a naturally-occurring precursor to neomycin A, neomycin B or neomycin C.

3. The method according to claim 2, wherein the neomycin analogue comprises a substituted-2-deoxystreptamine (2-DOS) linked to two to four sugars, wherein each sugar is a pentose or hexose.

4. The method according to claim 3, wherein the neomycin analogue is a member of the neomycin, paromomycin or lividomycin aminoglycoside family.

5. The method according to claim 4, wherein the neomycin analogue comprises a glucosyl residue attached to the 4 position of the 2-DOS moiety, which glucosyl residue comprises an amino group at each of the 2 and 6 positions.

6. The method according to claim 4, wherein the neomycin analogue comprises a 2-DOS and a 2,6-diamino-2-6-dideoxy-D-glucose attached to the 4 position of 2-DOS.

7. The method according to claim 5, wherein the neomycin analogue is nebramine, gentamine C.sub.1, gentamine C.sub.2, gentamine C.sub.1a, ribostamycin, or xylostasin.

8. The method according to claim 1, wherein the neomycin analogue is an inhibitor of phospholipase C.

9. The method according to claim 1, wherein the neomycin analogue is an inhibitor of nuclear translocation of an angiogenic factor.

10. The method according to claim 1, wherein the neomycin analogue is an inhibitor of endothelial cell proliferation induced by an angiogenic factor.

11. The method according to claim 1, wherein the neomycin analogue is an inhibitor of angiogenesis in the chorioallantoic membrane of chick embryo induced by an angiogenic factor.

12. The method according to claim 9, 10, or 11, wherein the angiogenic factor is angiogenin, acidic fibroblast growth factor, basic fibroblast growth factor, epidermal growth factor, tumor growth factor-alpha, tumor growth factor-beta, tumor necrosis factor-alpha or vascular endothelial growth factor.

13. The method according to claim 1 in which the subject is a human.

14. The method according to claim 1 in which the pathological angiogenesis or proliferation of endothelial cells is associated with a disease selected from the group consisting of fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, acoustic neuroma, neurofibroma, trachoma and pyogenic granulomas.

15. The method according to claim 14 wherein the disease is breast cancer.

16. The method according to claim 14 wherein the disease is prostate cancer.

17. The method according to claim 1 in which the pathological angiogenesis or proliferation of endothelial cells is associated with a disease selected from the group consisting of acute lymphocytic leukemia and acute myelocytic leukemia, chronic leukemia, polycythemia vera, lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, and heavy chain disease.

18. The method according to claim 1 in which the pathological anziogenesis or proliferation of endothelial cells is associated with a disease selected from the group consisting of acne rosacea, atopic keratitis, chemical burns, contact lens overwear, corneal graft rejection, diabetic retinopathy, epidemic keratoconjunctivitis, fungal ulcers, Herpes simplex infections, herpes zoster infections, Kaposi sarcoma, lipid degeneration, marginal keratolysis, Mooren ulcer, neovascular glaucoma and retrolental fibroplasia, periphigoid radial keratotomy, phylectenulosis, polyarteritis, protozoan infections, pterygium keratitis sicca, retinopathy of prematurity, rheumatoid arthritis, sjogrens, scleritis, Steven's Johnson disease, superior limbic keratitis, syphilis, systemic lupus, Terrien's marginal degeneration, trauma, vitamin A deficiency, and Wegeners sarcoidosis.

19. The method according to claim 1 in which the pathological angiogenesis or proliferation of endothelial cells is associated with a disease selected from the group consisting of artery occlusion, Bechets disease, Bests disease, chronic retinal detachment, chronic uveitis/vitritis, carotid obstructive disease, diabetic retinopathy, Eales disease, hyperviscosity syndromes, retinitis, choroiditis, Lyme's disease, macular degeneration, optic pits, Pagets disease, pars planitis, post-laser complications, presumed ocular histoplasmosis, pseudoxanthoma elasticum, retinopathy of prematurity, sickle cell anemia, sarcoid, Stargarts disease, syphilis, systemic lupus erythematosis, toxoplasmosis, trauma, vein occlusion, rubeosis, and proliferative vitreoretinopathy.

20. The method according to claim 1 in which the pathological angiogenesis or proliferation of endothelial cells is associated with a disease selected from the group consisting of Crohn's disease and ulcerative colitis, psoriasis, rheumatoid arthritis, sarcoidosis, hemangiomas, Osler-Weber-Rendu disease, hereditary hemorrhagic telangiectasia, and acquired immune deficiency syndrome.

21. The method according to claim 14, 15, 16, or 17 which comprises additionally administering an anti-neoplastic agent to the subject.

22. The method according to claim 21, wherein the anti-neoplastic agent is selected from the group consisting of docetaxel, etoposide, irontecan, paclitaxel, teniposide, topotecan, vinblastine, vincristine, and vindesine, busulfan, improsulfan, piposulfan, aziridines, benzodepa, carboquone, meturedepa, uredepa, altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, chlorambucil, chloraphazine, cyclophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, perfosfamide, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, temozolomide, aclacinomycinsa actinomycin F.sub.1, anthramycin, azaserine, bleomycins, cactinomycin, carubicin, carzinophilin, chromomycins, dactinomycin, daunorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, idarubicin, menogaril, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, pirarubicin, plicamycin, porfiromycin, puromycin, streptonigrin, streptozocin, tubercidin, zinostatin, zorubicin, denopterin, edatrexate, methotrexate, piritrexim, pteropterin, Tomudex.RTM., trimetrexate, cladribine, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, doxifluridine, emitefur, enocitabune, floxuridine, fluorouracil, gemcitabine, tegafur, L-asparaginase, interferon-.alpha., interferon-.beta., interferon-.gamma., interleukin-2, lentinan, propagermanium, PSK, roquinimex, sizofican, ubenimex, carboplatin, cisplatin, miboplatin, oxaliplatin, aceglarone, amsacrine, bisantrene, defosfamide, demecolcine, diaziquone, eflomithine, elliptinium acetate, etoglucid, fenretinide, gallium nitrate, hydroxyurea, lonidamine, miltefosine, mitoguazone, mitoxantrone, mopidamol, nitracine, pentostain, phenamet, podophyllinic acid 2-ethyl-hydrazide, procabazine, razoxane, sobuzoxane, spirogermanium, tenuzonic acid, triaziquone, 2,2',2"trichlorotriethylamine, urethan, calusterone, dromostanolone, epitiostanol, mepitiostane, testolacone, aminoglutethimide, mitotane, trilostane, bicalutamide, flutamide, nilutamide, droloxifene, tamoxifen, toremifene, aminoglutethimide, anastrozole, fadrozole, formestane, letrozole, fosfestrol, hexestrol, polyestradiol phosphate, buserelin, goserelin, leuprolide, triptorelin, chlormadinone acetate, medroxyprogesterone, megestrol acetate, melengestrol, porfimer sodium, batimastar, and folinic acid.

23. A method of inhibiting pathological angiogenesis or proliferation of endothelial cells in a subject, which method comprises administering to the subject a therapeutic amount of (a) neomycin or an analogue thereof, and (b) an anti-angiogenic agent that is not neomycin or an analogue thereof, sufficient to inhibit pathological angiogenesis or proliferation of endothelial cells.

24. The method according to claim 23, wherein the anti-angiogenic agent is selected from the group consisting of thalidomide, 2-methoxyestradiol, endostatin, angiostatin, platelet factor-4, dextran sulfate, beta-1,3-glucan sulfate, interferon-alpha, interleukin-12, 22-oxa-1 .alpha.,25-dihydroxyvitamin D.sub.2, monoclonal antibody 26-2F, monoclonal antibody 36U, peptide comprising the sequence NH.sub.2-Val-Phe-Ser-Val-Arg-Val-Ser-Ile-Leu-Val-Phe-COOH (SEQ ID NO. 1), peptide comprising the sequence NH.sub.2-Leu-Leu-Phe-Leu-Pro-Leu-Gly-Val-Ser-Leu-Leu-Asp-Ser-COOH (SEQ ID NO. 2), human placental ribonuclease inhibitor, peptide comprising the sequence NH.sub.2-Tyr-Ser-Val-Trp-Ile-Gly-Gly-Ser-Ile-Leu-Ala-Ser-Leu-Ser-Thr-Phe-Gln-Gln-Met-Trp-Ile-Ser-Lys-COOH (SEQ ID NO. 4), peptide comprising the sequence NH.sub.2-Ala-Gln-Leu-Ala-Gly-Glu-Cys-Arg-Glu-Asn-Val-Cys-Met-Gly-Ile-Glu-Gly-Arg-COOH (SEQ ID NO. 3), nucleotide comprising the sequence 5'-CGGACGAATGCTTTGATGTTGTGCTGGACCAGCGTTCATTCTCA-3' (SEQ ID NO. 5), anthracycline, 15-deoxyspergualin, D-penicillamine, eponemycin, fumagillin, AGM-1470, herbimycin A, rapamycin, CAI, CM101, and marimastat.

25. A pharmaceutical composition comprising a therapeutically effective amount of (a) neomycin or an analogue thereof, and (b) an anti-angiogenic agent that is not neomycin or an analogue thereof, together with a pharmaceutically acceptable carrier, said amount sufficient to suppress pathological angiogenesis or proliferation of endothelial cells in a subject.

26. The pharmaceutical composition of claim 25, wherein the neomycin analogue is (a) neomycin A, neomycin B, or neomycin C; (b) a complex comprising neomycin A, neomycin B, or neomycin C; (c) an aminoglycoside having a structure substantially similar to that of neomycin A, neomycin B or neomycin C; (d) a chemical or biological breakdown product of neomycin A, neomycin B or neomycin C; (e) a derivative of neomycin A, neomycin B or neomycin C; or (f) a naturally-occurring precursor to neomycin A, neomycin B or neomycin C.

27. The pharmaceutical composition of claim 26, wherein the neomycin analogue comprises a substituted-2-deoxystreptamine (2-DOS) linked to two to four sugars, wherein each sugar is a pentose or hexose.

28. The pharmaceutical composition of claim 27, wherein the neomycin analogue is a member of the neomycin, paromomycin or lividomycin aminoglycoside family.

29. The pharmaceutical composition of claim 28, wherein the neomycin analogue comprises a glucosyl residue attached to the 4 position of the 2-DOS moiety, which glucosyl residue comprises an amino group at each of the 2 and 6 positions.

30. The pharmaceutical composition of claim 29, wherein the neomycin analogue comprises a 2-DOS and a 2,6-diamino-2-6-dideoxy-D-glucose attached to the 4 position of 2-DOS.

31. The pharmaceutical composition of claim 29, wherein the neomycin analogue is nebramine, gentamine C.sub.1, gentamine C.sub.2, gentamine

C.sub.1a, ribostamycin, or xylostasin.

32. The pharmaceutical composition of claim 25, wherein the neomycin analogue is an inhibitor of nuclear translocation of an angiogenic factor.

33. The pharmaceutical composition of claim 25, wherein the neomycin analogue is an inhibitor of phospholipase C.

34. The pharmaceutical composition of claim 25, wherein the neomycin analogue is an inhibitor of endothelial cell proliferation induced by an angiogenic factor.

35. The pharmaceutical composition of claim 25, wherein the neomycin analogue is an inhibitor of angiogenesis in the chorioallantoic membrane of chick embryo induced by an angiogenic factor.

36. The pharmaceutical composition of claim 32, 34 or 35, wherein the angiogenic factor is angiogenin, acidic fibroblast growth factor, basic fibroblast growth factor, epidermal growth factor, tumor growth factor-alpha, tumor growth factor-beta, tumor necrosis factor-alpha, vascular endothelial growth factor, platelet-derived growth factor, platelet-derived endothelial cell growth factor, placental growth factor, hepatocyte growth factor, platelet activating factor, insulin-like growth factor, interleukin-8, or granulocyte-colony stimulating factor.

37. The pharmaceutical composition of claim 25 in which the subject is a human.

38. The pharmaceutical composition of claim 25 in which the anti-angiogenic factor is selected from the group consisting of thalidomide, 2-methoxyestradiol, endostatin, angiostatin, platelet factor-4, dextran sulfate, beta-1,3-glucan sulfate, interferon-alpha, interleukin-12, 22-oxa- 1 .alpha., 25-dihydroxyvitamin D.sub.2, monoclonal antibody 26-2F, monoclonal antibody 36U, peptide comprising the sequence NH.sub.2-Val-Phe-Ser-Val-Arg-Val-Ser-Ile-Leu-Val-Phe-COOH (SEQ ID NO. 1), peptide comprising the sequence NH.sub.2-Leu-Leu-Phe-Leu-Pro-Leu-Gly-Val-Ser-Leu-Leu-Asp-Ser-COOH (SEQ ID NO. 2), human placental ribonuclease inhibitor, peptide comprising the sequence NH.sub.2-Tyr-Ser-Val-Trp-Ile-Gly-Gly-Ser-Ile-Leu-Ala-Ser-Leu-Ser-Thr-Phe-Gln-Gln-Met-Trp-Ile-Ser-Lys-COOH (SEQ ID NO. 4), peptide comprising the sequence NH.sub.2-Ala-Gln-Leu-Ala-Gly-Glu-Cys-Arg-Glu-Asn-Val-Cys-Met-Gly-Ile-Glu-Gly-Arg-COOH (SEQ ID NO. 3), nucleotide comprising the sequence 5'-CGGACGAATGCTTTGATGTTGTGCTGGACCAGCGTTCATTCTCA-3'(SEQ ID NO. 5), anthracycline, 15-deoxyspergualin, D-penicillamine, eponemycin, fumagillin, AGM-1470, herbimycin A, rapamycin, CAI, CM101, and marimastat.

39. A pharmaceutical composition comprising a therapeutically effective amount of (a) neomycin or an analogue thereof, and (b) an anti-neoplastic agent, together with a pharmaceutically acceptable carrier, said amount sufficient to treat an angiogenesis-related disease which is a tumor in a subject.

40. The pharmaceutical composition of claim 39, wherein the neomycin analogue is (a) neomycin A, neomycin B, or neomycin C; (b) a complex comprising neomycin A, neomycin B, or neomycin C; (c) an aminoglycoside having a structure substantially similar to that of neomycin A, neomycin B or neomycin C; (d) a chemical or biological breakdown product of neomycin A, neomycin B or neomycin C; (e) a derivative of neomycin A, neomycin B or neomycin C; or (f) a naturally-occurring precursor to neomycin A, neomycin B or neomycin C.

41. The pharmaceutical composition of claim 40, wherein the neomycin analogue comprises a substituted-2-deoxystreptamine (2-DOS) linked to two to four sugars, wherein each sugar is a pentose or hexose.

42. The pharmaceutical composition of claim 41, wherein the neomycin analogue is a member of the neomycin, paromomycin or lividomycin aminoglycoside family.

43. The pharmaceutical composition of claim 42, wherein the neomycin analogue comprises a glucosyl residue attached to the 4 position of the 2-DOS moiety, which glucosyl residue comprises an amino group at each of the 2 and 6 positions.

44. The pharmaceutical composition of claim 43, wherein the neomycin analogue comprises a 2-DOS and a 2,6-diamino-2-6-dideoxy-D-glucose attached to the 4 position of 2-DOS.

45. The pharmaceutical composition of claim 43, wherein the neomycin analogue is nebramine, gentamine C.sub.1, gentamine C.sub.2, gentamine C.sub.1a, ribostamycin, or xylostasin.

46. The pharmaceutical composition of claim 39, wherein the neomycin analogue is an inhibitor of nuclear translocation of an angiogenic factor.

47. The pharmaceutical composition of claim 39, wherein the neomycin analogue is an inhibitor of phospholipase C.

48. The pharmaceutical composition of claim 39, wherein the neomycin analogue is an inhibitor of endothelial cell proliferation induced by an angiogenic factor.

49. The pharmaceutical composition of claim 39, wherein the neomycin analogue is an inhibitor of angiogenesis in the chorioallantoic membrane of chick embryo induced by an angiogenic factor.

50. The pharmaceutical composition of claim 46, 48 or 49, wherein the angiogenic factor is angiogenin, acidic fibroblast growth factor, basic fibroblast growth factor, epidermal growth factor, tumor growth factor-alpha, tumor growth factor-beta, tumor necrosis factor-alpha, vascular endothelial growth factor, platelet-derived growth factor, platelet-derived endothelial cell growth factor, placental growth factor, hepatocyte growth factor, platelet activating factor, insulin-like growth factor, interleukin-8, or granulocyte-colony stimulating factor.

51. The pharmaceutical composition of claim 39 in which the subject is a human.

52. The pharmaceutic composition of claim 39, wherein the anti-neoplastic agent is selected from the group consisting of docetaxel, etoposide, trontecan, paclitaxel, teniposide, topotecan, vinblastine, vincristine, and vindesine, busulfan, improsulfan, piposulfan, aziridines, benzodepa, carboquone, meturedepa, uredepa, altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, chlorambucil, chloraphazine, cyclophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, perfosfarmide, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, temozolomide, aclacinomycinsa actinomycin F.sub.1, anthramycin, azaserine, bleomycins, cactinomycin, carubicin, carzinophilin, chromomycins, dactinomycin, daunorubicin,

6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, idarubicin, menogaril, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, pirarubicin, plicamycin, porfiromycin, puromycin, streptonigrin, streptozocin, tubercidin, zinostatin, zorubicin, denopterin, edatrexate, methotrexate, piritrexim, pteropterin, Tomudex.RTM., trimetrexate, cladribine, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, doxifluridine, emitefur, enocitabune, floxuridine, fluorouracil, gemcitabine, tegafur, L-asparaginase, interferon-.alpha., interferon-.beta., interferon-.gamma., interleukin-2, lentinan, propagermanium, PSK, roquinimex, sizofican, ubenimex, carboplatin, cisplatin, miboplatin, oxaliplatin, aceglarone, amsacrine, bisantrene, defosfamide, demecolcine, diaziquone, eflornithine, elliptinium acetate, etoglucid, fenretinide, gallium nitrate, hydroxyurea, lonidamine, miltefosine, mitoguazone, mitoxantrone, mopidamol, nitracine, pentostain, phenamet, podophyllinic acid 2-ethyl-hydrazide, procabazine, razoxane, sobuzoxane, spirogermanium, tenuzonic acid, triaziquone, 2,2',2"trichlorotriethylamine, urethan, calusterone, dromostanolone, epitiostanol, mepitiostane, testolacone, aminoglutethimide, mitotane, trilostane, bicalutamide, flutamide, nilutamide, droloxifene, tamoxifen, toremifene, aminoglutethimide, anastrozole, fadrozole, formestane, letrozole, fosfestrol, hexestrol, polyestradiol phosphate, buserelin, goserelin, leuprolide, triptorelin, chlormadinone acetate, medroxyprogesterone, megestrol acetate, melengestrol, porfimer sodium, batimastar, and folinic acid.

53. A method for selecting a neomycin analogue for use in inhibiting angiogenesis or proliferation of endothelial cells, comprising testing the neomycin analogue for activity for inhibiting angiogenesis.

54. The method according to claim 53, which comprises (a) incubating a first culture of endothelial cells with the neomycin analogue and an angiogenic factor. in a growth medium, and incubating a second culture of endothelial cells with the angiogenic factor in the growth medium lacking the neomycin analogue, wherein the angiogenic factor is labeled; (b) determining the amounts of angiogenic factor present in the nuclei of cells in the first and the second cultures; and (c) selecting for use in treating the angiogenesis-related disease, the neomycin analogue that inhibits nuclear translocation of the angiogenic factor in cells of the first culture by at least 10% of the amount of the angiogenic factor translocated to the nuclei of the cells in the second culture.

55. The method according to claim 53, which comprises (a) incubating a first culture of endothelial cells with the neomycin analogue in a growth medium, and incubating a second culture of endothelial cells in a growth medium lacking the neomycin analogue; (b) incubating the first and the second cultures with an angiogenic factor in the growth medium, wherein the angiogenic factor is labeled; (c) determining the amount of angiogenic factor present in the nuclei of cells in the first and the second cultures; and (d) selecting for use in treating the angiogenesis-related disease, the neomycin analogue that inhibits nuclear translocation of the angiogenic factor in the cells of the first culture by at least 10% of the amount of nuclear translocation of the angiogenic factor in the cells of the second culture.

56. The method according to claim 53, which comprises (a) incubating a first culture of endothelial cells with the neomycin analogue and an angiogenic factor in a growth medium, incubating a second culture of endothelial cells with the neomycin analogue in the growth medium lacking the angiogenic factor, incubating a third culture of endothelial cells with the angiogenic factor in the growth medium lacking the neomycin analogue, incubating a fourth culture of endothelial cells in the growth medium lacking the neomycin analogue and the angiogenic factor; (b) determining the cell numbers of the first, the second, the third and the fourth cultures; and (c) selecting for use in treating the angiogenesis-related disease, the neomycin analogue that reduces the increase in the cell number in the second culture over the cell number in the first culture to less than about 75% of the increase in cell number of the third culture over the cell number of the fourth culture.

57. The method according to claim 53, which comprises (a) contacting the chorioallantoic membrane of a first group of chick embryos with the neomycin analogue and an angiogenic factor, contacting the chorioallantoic membrane of a second group of chick embryos with the neomycin analogue but not the angiogenic factor, contacting the chorioallantoic membrane of a third group of chick embryos with the angiogenic factor but not the neomycin analogue, and contacting the chorioallantoic membrane of a fourth group of chick embryos with a solution lacking the neomycin analogue and the antigenic factor; (b) incubating the first, the second, the third and the fourth groups of chick embryos; (c) determining the numbers of embryos having an angiogenic response in the first, the second, the third and the fourth groups of embryos; and (d) selecting for use in treating the angiogenesis-related disease, the neomycin analogue that reduces the increase in the number of embryos exhibiting an angiogenic response in the second group of embryos over the number of embryos exhibiting an angiogenic response in the first group of embryos to less than about 75% of the increase in the number of embryos exhibiting an angiogenic response in the third group of embryos over the number of embryos exhibiting an angiogenic response in the fourth group of embryos.

58. The method according to any one of claims 53 to 57, wherein the neomycin analogue is (a) neomycin A, neomycin B, or neomycin C; (b) a complex comprising neomycin A, neomycin B, or neomycin C; (c) an aminoglycoside having a structure substantially similar to that of neomycin A, neomycin B or neomycin C; (d) a chemical or biological breakdown product of neomycin A, neomycin B or neomycin C; (e) a derivative of neomycin A, neomycin B or neomycin C; or (f) a naturally-occurring precursor to neomycin A, neomycin B or neomycin C.

59. The method according to claim 58, wherein the neomycin analogue comprises a substituted-2-deoxystreptamine (2-DOS) linked to two to four sugars, wherein each sugar is a pentose or hexose.

60. The method according to claim 59, wherein the neomycin analogue is a member of the neomycin, paromomycin or lividomycin aminoglycoside family.

61. The method according to claim 60, wherein the neomycin analogue comprises a glucosyl residue attached to the 4 position of the 2-DOS moiety, which glucosyl residue comprises an amino group at each of the 2 and 6 positions.

62. The method according to claim 61, wherein the neomycin analogue comprises a 2-DOS and a 2,6-diamino-2-6-dideoxy-D-glucose attached to the 4 position of 2-DOS.

63. The method according to any one of claims 53 to 57, wherein the angiogenic factor is angiogenin, acidic fibroblast growth factor, basic fibroblast growth factor, epidermal growth factor, tumor growth factor-alpha, tumor growth factor-beta, tumor necrosis factor-alpha, vascular endothelial growth factor, platelet-derived growth factor, platelet-derived endothelial cell growth factor, placental growth factor, hepatocyte growth factor, platelet activating factor, insulin-like growth factor, interleukin-8, or granulocyte-colony stimulating factor.

INCL INCLM: 514/039.000

INCLS: 514/002.000; 536/013.200
NCL NCLM: 514/039.000
NCLS: 514/002.000; 536/013.200
IC [7]
ICM: A61K031-37
EXF 514/39; 536/13.2
ARTU 164
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 40 OF 40 USPATFULL
AN 2000:37315 USPATFULL
TI Injection-molding apparatus and method of injection-molding
IN Abe, Masaharu, Otake, Japan
Takaragi, Shigeru, Otake, Japan
Yamamoto, Hiroshi, Otake, Japan
Nakamura, Kyoichi, Otake, Japan
Sasaki, Osamu, Otake, Japan
PA Toda Kogyo Corporation, Japan (non-U.S. corporation)
PI US 6042757 20000328 <--
AI US 1998-84921 19980528 (9)
PRAI JP 1997-157552 19970529
DT Utility
FS Granted
REP US 4209290 Jun 1980 425/547.000 Rees et al.
US 4246225 Jan 1981 264/336.000 Ninneman
US 4514166 Apr 1985 264/336.000 Ichizawa et al.
US 4836767 Jun 1989 Schad et al.
US 5181971 Jan 1993 264/429.000 Ohtsuka
US 5384957 Jan 1995 029/895.320 Mohri et al.
US 5453224 Sep 1995 264/427.000 Kuroda
US 5514309 May 1996 264/336.000 Williamson et al.
US 5570167 Oct 1996 264/108.000 Kuroda
US 5653924 Aug 1997 264/334.000 Brun, Jr. et al.
EP 283644 Sep 1988
EP 718084 Jun 1996
EXNAM Primary Examiner: Heitbrink, Jill L.
LREP Nixon & Vanderhye
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN 9 Drawing Figure(s); 5 Drawing Page(s)
AB An injection-molding device including an injection machine, a mold unit connected to the injection machine having separable molds defining a cavity for forming a molded product, and chucks next to the mold unit for removing a molded product from the mold. The molded product is initially coolied in the mold cavity then again cooled after removal from the mold unit. Plural chucks are advanced into and retreated from a region defined by the open molds, the chucks being a pair of blocks grasping the surface of the molded product, each block having a circulating path through which a heating medium is passed to cool the grasping surface. The injection-molding apparatus produces articles having high dimensional accuracy, for example, electronic parts such as a magnet roll or the like.

SUMM BACKGROUND OF THE INVENTION

The present invention relates to an injection-molding apparatus and a method of injection-molding, and more particularly, to an injection-molding apparatus for forming a molded product from a molding material comprising a thermoplastic resin and an inorganic filler, which is capable of not only reducing costs for production facilities and shortening an injection-molding cycle time, thereby achieving a high productivity, but also effectively preventing deformation of the molded product, and a method for injection-molding a molding material comprising a thermoplastic resin and an inorganic filler using such an apparatus.

The injection-molding apparatus and method of injection-molding according to the present invention are useful for the production of such articles required to have a high dimensional accuracy, for example, electronic parts such as a magnet roll or the like.

In general, molded products such as magnet rolls have been produced by subjecting a molding material comprising a thermoplastic resin such as a polyamide resin or the like and an inorganic filler such as ferrite particles or iron oxide particles to an injection-molding process. A molding cycle of such an injection-molding cycle comprises steps of clamping, injecting, dwelling, cooling, mold-opening and removing the molded product from the mold. In the production of magnet roll, etc., these molded products have been required to have a high dimensional accuracy. On the other hand, various methods for reducing the time required for conducting the above-mentioned steps, especially a cooling step, have been studied in order to achieve a high productivity.

Meanwhile, in the above-mentioned production, if the cooling time in the mold is shortened, the molded product cannot be sufficiently cooled in the mold before its removal. This causes internal strain of the molded product generated upon injection-molding to be released, so that the molded product undergoes deformation such as warpage or bend. In addition, there have been proposed a method of shortening the cooling time by lowering the temperature of the mold. However, in the case where the temperature of the mold is too low, a resin flowing on an inner surface of the mold is abruptly solidified upon injection thereof, so that generation of strain in the molded product is further promoted.

Therefore, there has been recently proposed a method of shortening a molding cycle time, which method is called "OCI (Outside Cooling Injection)" (refer to the magazine "PLASTICS" Vol. 45, No. 45, pp. 37-41(1994) and Japanese Patent Application Laid-open (KOKAI) No. 7-9498(1995)). In the OCI method, there have been used two molds (A and B), and a resin is first injected into the mold A and then into the mold B. That is, (1) after completion of the injection at the mold A, the resin is injection-molded in the mold B. (2) During the injection in the mold B, a molded product obtained at the mold A is cooled and removed therefrom. (3) After completion of the injection at the mold B, the resin is injected again into a vacant cavity of the mold A. According to the OCI method, the above-mentioned molding operations are repeated alternately at the molds A and B, thereby ensuring a sufficient cooling time and enhancing a productivity of molded products.

However, in the OCI method, at least two identical molds and a large-size injection unit for injecting the resin to the respective molds are necessary, thereby considerably increasing costs for production facilities. The OCI method actually requires a high cost exceeding an upper limit of desired production cost, so that it becomes extremely difficult to adopt the OCI method.

As a result of the present inventors' earnest studies for solving the above-mentioned problems in prior arts, it has been found that in an injection-molding apparatus comprising an injection machine and a mold unit, by providing a holding means comprising a plural of chucks, disposed adjacent to the mold unit having a cavity (or cavities) for removing the molded product from the mold unit, wherein the ratio of the number of the chuck to the number of the cavity of the mold unit is set to a value not less than the ratio of operation time of each chuck to operation time of the mold unit, not only the reduction of costs for production facilities and the shortening of an injection-molding cycle time can be achieved, but also the effective prevention of the deformation of the molded product can be attained. On the basis of the above-mentioned finding, the present invention has been achieved.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide an injection-molding apparatus, which are capable of not only reducing costs for production facilities and shortening an injection-molding cycle time, thereby achieving a high productivity, but also effectively preventing deformation of the molded product, and a method for injection-molding a molding material using such an apparatus.

It is another object of the present invention to provide an injection-molding apparatus, which are capable of shortening an operation time in a mold while ensuring a sufficient time for cooling a molded product, thereby producing electronic parts having a high dimensional accuracy without deformation, such as magnet rolls, and a method for injection-molding a molding material using such an apparatus.

To accomplish the aim, in a first aspect of the present invention, there is provided an injection-molding apparatus comprising:

an injection machine;

a mold unit connected to the injection machine and constituted by separable molds which constitutes therein a cavity for forming a molded product; and

a holding means disposed adjacent to the mold unit for removing the molded product from the mold unit, comprising a plural of chucks adapted to advance into and retreat from a region defined between the opened molds of the mold unit,

the molded product being subjected to a primary cooling in the cavity of the mold unit and then being subjected to a secondary cooling after removed from the mold unit, and

the ratio of the number of the chuck to the number of the cavity of the mold unit being set to a value not less than the ratio of operation time of each chuck to operation time of the mold unit.

In the second aspect of the present invention, there is provided an injection-molding apparatus comprising:

an injection machine;

a mold unit connected to the injection machine and constituted by separable molds which constitutes therein a cavity for forming a molded product; and

a holding means disposed adjacent to the mold unit for removing the molded product from the mold unit, comprising a plural of chucks adapted to advance into and retreat from a region defined by the opened molds of the mold unit,

the molded product being subjected to a primary cooling in the cavity of the mold unit held at the closed position and then being subjected to a secondary cooling after removed from the mold unit, to form a substantially bar-like magnet roll comprising a thermoplastic resin and an inorganic filler, and

ratio of the number of the chuck to the number of the cavity being set to a value not less than a ratio of operation time of each chuck to operation time of the mold unit; each of the chucks comprising a pair of blocks being opposed to each other and each having a grasping surface which can be brought into a face contact with an outer peripheral surface of the molded product; and each of the blocks being provided therein with a circulating path through which a heating medium is passed to cool the grasping surface.

In a third aspect of the present invention, there is provided a method for injecting molding a molding material, comprising:

injecting the molding material comprising a thermoplastic resin and an inorganic filler from an injection unit into a cavity of a mold unit to form a molded product;

subjecting the molded product to a primary cooling in the cavity;

removing the molded product from the mold unit using chucks as a holding means; and

subjecting the molded product to a secondary cooling while holding the molded product by the chucks,

the ratio of the number of the chuck to the number of the cavity being set to a value not less than the ratio of operation time of each chuck to operation time of the mold unit.

DRWD BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a side view schematically showing an injection-molding apparatus according to the present invention;

FIG. 2(a) is a side view showing a whole structure of a holding means according to the present invention;

FIG. 2(b) is a front view of the holding means shown in FIG. 2(a);

FIG. 3(a) is a plan view showing one preferred embodiment of chucks of the holding means according to the present invention;

FIG. 3(b) is a front view of the chucks shown in FIG. 3(a);

FIGS. 4(a) to FIG. 4(c) are cross-sectional views of various molded products having an approximately bar-like shape, taken along the direction perpendicular to an axial direction of each molded product; and

FIG. 5 is a flow diagram showing respective operations of an injection-molding process according to the present invention, by means of the relationship of the temperature of a molded product and time.

DETD DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the injection-molding apparatus of the present invention, by controlling the ratio between the number of the chuck and the number of the cavity of the mold unit to a value not less than the ratio between the operation times of the mold unit and each chuck, it is possible to eliminate an idling time of the mold unit and assure a sufficient time for cooling the molded product in the holding means.

In the injection-molding apparatus of the present invention, in order to more effectively conduct the injection-molding, it is preferred to use a injection machine comprising a kneader for melting and kneading a molding material, and an injection unit for injecting the kneaded material in cavities of the mold unit while keeping the kneaded material in a molten state.

In addition, in the injection-molding apparatus of the present invention, it is preferred that in order to more effectively cool the molded product removed, each of the chucks comprising a pair of blocks being opposed to each other and each having a grasping surface which can be brought into a close face contact with an outer peripheral surface of the molded product, and each of the blocks be provided therein with a circulating path through which a heating medium is passed to cool the grasping surface.

Further, the injection-molding apparatus of the present invention can be especially suitably applied to the production of a molded product made of a specific molding material. As the molding material, there may be used materials comprising at least one thermoplastic resin selected from the group consisting of a polyamide resin, a polyphenylene sulfide resin, an ethylene-ethyl acrylate resin, an ethylene-ethyl methacrylate resin, a liquid crystalline polymer and a chlorinated polyethylene resin, and at least one inorganic filler selected from the group consisting of ferrite particles such as hard ferrite particles or soft ferrite particles, iron oxide particles, and iron metal particles. As the molded product, there may be exemplified a substantially bar-like magnet roll.

The magnet roll is an electronic part used in electrophotographic machines, printers or the like, and can be produced by molding the molding material into approximately bar-like products having various cross-sectional shapes, as shown in FIG. 4(a) to FIG. 4(c). In case of relative small-size magnet rolls, the size of the magnet rolls may be, for example, a maximum diameter of about 8 to about 11 mm and a length (axial length) of about 210 to about 260 mm.

In the method for injection-molding the molding material according to the present invention, by controlling the ratio between the number of the chuck and the number of the cavity of the mold unit to a value not less than the ratio between the operation times of the mold unit and each chuck, it is possible to eliminate an idling time of the mold unit and assure a sufficient time for cooling the molded product in the holding means.

Further, in the injection-molding method of the present invention, it is preferred that in order to continuously conduct the molding method, an apparatus comprising a kneader and an injection unit is used as the injection machine, a molding material is melted and kneaded in the kneader, and the obtained kneaded material is injected from the injection unit into a cavity (or cavities) of the mold unit while keeping the kneaded material in a molten state.

Further, in the injection-molding method of the present invention, when the molded product is removed from the mold unit, it is preferred to control the difference between the temperature of the mold unit and the temperature of the holding means to 0 to 50.degree. C. by circulating a heating medium through the chucks. In accordance with such a preferred embodiment, the molded product removed from the mold unit can be more effectively cooled while preventing deformation thereof.

The preferred embodiment of the injection-molding apparatus according to the present invention will be explained by referring to FIGS. 1 to 5.

As shown in FIG. 1, the injection-molding apparatus according to the present invention is adapted to subject an injection-molded product to a primary cooling while keeping the molded product in cavities of a mold unit 1. Thereafter, the molded product is removed from the mold unit 1 and then subjected to a secondary cooling.

As shown in FIG. 1, the injection-molding apparatus according to the present invention comprises a mold unit 1 constituted by separable molds, which constitutes cavities therein, an injection machine 2 connected to the mold unit 1, and a holding means 3 disposed adjacent to the mold unit 1 for removing the obtained molded product from the mold unit 1. The mold unit 1 may be constituted by vertically separable upper and lower molds. However, it is preferred that in order to simplify the structure for removal of the molded product, the mold unit 1 be constituted by horizontally separable right and left molds.

The injection machine 2 comprising a kneader for melting and kneading a molding material, and an injection unit for injecting the kneaded material into the mold unit 1 while keeping the kneaded material in a molten state, for example, as described in Japanese Patent Publication (KOKOKU) No. 7-106586(1995). In such an injection machine 2, a kneader 21 and an injection unit 22 may be used in combination, so that it is possible to continuously conduct a series of operations from melting and kneading of the molding material up to injection thereof. By adopting such a machine, the molding operation can be more effectively conducted.

The kneader 21 of the injection machine 2 comprises a cylinder provided on its outer periphery with a heater, a hopper 21b arranged on a rear end side of the cylinder for feeding a raw molding material into the cylinder, a discharge nozzle attached to the front end (tip end) of the cylinder for discharging the kneaded material therefrom, and a screw inserted into the cylinder for delivering the kneaded material. The molding material is fed through the hopper 21b into the cylinder, and heated and melted therein. The molten molding material is then kneaded and transported by driving the screw, and discharged through the discharge nozzle into the injection unit 22. In addition, the injection unit 22 comprises a casing provided on its outer periphery with a heater, a vent port formed on a rear end of the casing, an injecting nozzle disposed on a front end (tip end) of the casing, and a screw inserted into the casing for pressurizing the kneaded material. The kneaded material, i.e., molten molding material is supplied through the discharge nozzle of the kneader 21 into the injection unit 22, and a predetermined amount of the molten molding material is intermittently injected by the rotation, and advance and retreat operations of the screw.

As shown in FIG. 1, the mold unit 1 is constituted by a stationary mold 11 and a movable mold 12. When closed in a mating manner, these molds constitute (form) therein a cavity corresponding to an outer shape of a magnet roll to be molded. That is, the mold unit 1 used herein has an approximately similar structure to those of known mold units, and is sequentially formed on an inside thereof with a runner, a gate and a mold cavity. The runner is connected with the nozzle of the injection unit 22 which is disposed so as to contact a base end (a side wall) of the stationary mold 11.

Incidentally, a plurality of the cavities is formed in the mold of the mold unit 1 as occasion demands. In the case where relatively small products such as magnet rolls are to be molded, for example, two mold cavities to which the molding material can be simultaneously injected by a branched runner formed in the mold of the mold unit 1.

Further, a flowing path for heating medium to control the temperature thereof are also formed in the molds. For example, the temperature of the molds can be controlled by the heating medium to about 90 to about 120.degree. C.

In addition, the movable mold 12 which can be advanced to and retreated from the stationary mold 11, is provided at its rear (base) end with an ejector pin capable of projecting toward the stationary mold upon opening of the molds to separate the molded magnet roll from the movable mold 12. Further, a exciting device, for example, a permanent magnet is disposed and embedded in the molds to apply a magnetic force to the molded magnet roll for magnetization thereof. In general, in view of shape of the magnet roll and direction of magnetic field applied thereto, a plurality of permanent magnets may be arranged so as to surround the cavity.

As shown in FIG. 2, the holding means comprises a plural of chucks which can be advanced to and retreated from a region formed between the molds of the mold unit 1 held in the opened position. Specifically, the holding means is constituted by a hand mechanism 3. The hand mechanism 3 comprises a support 31 uprightly provided at a side of the stationary mold 11 of the mold unit 1; a first horizontal linear guide 32 provided at an upper end of the support 31; a second horizontal linear guide 33 mounted horizontally movably onto the first linear guide 32 and extending in the direction perpendicular to the first linear guide 32; two sets of arms 34 mounted horizontally movably onto the second linear guide 33 and extending downwardly therefrom; and two sets of chucks 35 provided at a lower end of each arm 34 and rotatable around a horizontal axis.

More specifically, the chucks 35 are initially held above the mold unit 1 in its stand-by position, and by the combination of operations including horizontal movement of the second linear guide 33, horizontal movement and up and down movement of the two sets of arms 34 and rotational movement of the chucks 35, the chucks 35 are lowered and advanced into the region defined between the stationary mold 11 and movable mold 12 of the mold unit 1 which is held in the opened position, to grasp the molded magnet roll and transport the grasped magnet roll to the predetermined stand-by position.

The number of the chuck 35 is determined depending upon the number of the cavity, for example, in case of this embodiment, there are provided four chucks per two cavities in the mold. The two chucks 35 arranged on each arm 34 are adapted to rotate in association with the movement of each arm 34 by the operation of a cylinder unit mounted to a tip end of the arm 34. Further, as shown in FIG. 3, each chuck 35 is constituted by a pair of elongated blocks 35c such that longitudinal side surfaces thereof are opposed to each other. Each block 35c is attached to a guide bar and a cylinder unit which is reciprocally moveable in the direction perpendicular to the longitudinal direction of the block, so that the pair of blocks 35c can be moved so as to approach mutually or separate away from each other.

Further, in order to surely grasp or hold the magnet roll (molded product) and effectively cool the grasped magnet roll, a pair of the blocks 35c have grasping surfaces on opposed sides thereof, which grasping surfaces extend over a whole length of the molded magnet roll to be grasped and have such a shape capable of contacting with an outer peripheral surface of the molded magnet roll. In addition, each block 35c is formed therein with a circulating path through which a heating medium is passed to cool the grasping surface thereof.

For example, in the case where a cylindrical magnet roll is produced, the grasping surface on each block 35c of the chuck 35 has such a shape which allows the grasping surface to contact with an outer peripheral surface of the cylindrical body as evenly as possible when the two blocks 35c of the chuck 35 are caused to approach one another in order to grasp the cylindrical body. More specifically, in the case where a cylindrical magnet roll as shown in FIG. 4(a) is produced, the grasping surface of the chuck 35 is formed by a notch or recess having an approximately triangular or semi-circular shape in cross section taken along the direction perpendicular to a longitudinal axis of the cylindrical molded product. The maximum opening width of the notch or recess on the grasping surface may be approximately identical with a diameter of the magnet roll. When the grasping surface is formed by the notch or recess having such a maximum opening width, the magnet roll can be surely grasped, even immediately after molded.

In the apparatus according to the present invention, in order to eliminate an idling time of in-mold operation during the injection-molding process, the ratio of the number of chucks 35 to the number of the cavity in the mold unit 1 is set to a value not less than the ratio of the operation time of the chuck 35 to the operation time of the mold unit 1. In general, the number of the cavity in the mold unit 1 may be determined depending upon aimed output of molded products, and the number of chucks 35 may be determined depending upon the number of the cavity. The operation time of the mold unit 1 means a total time required for conducting respective in-mold operations including a clamping step, an injecting and dwelling step, a primary cooling step in mold, a mold-opening step and a removing step of the molded product from the mold. The operation time of the chuck 35 means a total time required for conducting operations subsequent to the removal of molded product up to secondary cooling in the chuck 35.

For example, assuming that the operation time (T1) in the mold unit 1 is about 40 seconds and the operation time (T2) in each chuck 35 is about 70 seconds, the ratio (T2/T1) therebetween is 70/40. Accordingly, the ratio (S2/S1) of the number (S2) of the chucks to the number (S1) of the cavity is set to a value not less than the T2/T1 ratio (70/40). If the number (S1) of the cavity is 2 sets, the number of the chuck 35 is set to not less than 3.5 sets, i.e., at least 4 sets.

Thus, by setting the ratio (S2/S1) between the number of the chuck and the number of the cavity to a value not less than the ratio (T2/T1) between the operation times of the mold unit 1 and each chuck 35, it is possible to continuously operate the mold unit 1. However, when the ratio (S2/S1) between the number of the chuck and the number of the cavity is set to a value excessively larger than the ratio (T2/T1) between the operation times of the mold unit and each chuck, i.e., when the number of the chuck 35 is too large relative to the number of the cavity, the cost required for production facilities may be disadvantageously increased. Therefore, it is most preferred that the ratio (S2/S1) between the number of the chuck and the number of the cavity be set to as close a value as possible, to the ratio (T2/T1) between the operation times of the mold unit and each chuck.

Next, the injection-molding process using the above-mentioned injection-molding apparatus in accordance with the present invention, will be explained by referring to FIG. 5 in addition to FIGS. 1 to 4. First, the above-mentioned molding material comprising a thermoplastic resin and an inorganic filler is fed through the hopper 21b into the kneader 21 of the injection machine 2. In the case where a magnet roll is produced, the molding material to be fed contains, for example, a nylon 6 resin and ferrite magnetic particles.

In the kneader 21 of the injection machine 2, the molding material is melted by operating the heater mounted on an outer periphery of the cylinder thereof. The molten molding material is kneaded and delivered by the screw in the cylinder, and then discharged through the discharge nozzle into the injection unit 22. Incidentally, the temperature of the molten molding material when kneaded may be about 290.degree. C.

When the molding material (kneaded material) is fed to the injection unit 22, the heater provided on an outer periphery of the casing of the injection unit 22 is operated to keep the molding material (kneaded material) in a molten state. The screw in the casing is rotated in

backward operational mode to temporarily store the molding material (kneaded material) in a tip end portion of the casing. At a predetermined timing, the rotation of the screw is reversed, and the screw is driven in forward operational mode to discharge therefrom a predetermined amount of the molding material under pressure. By such storage and discharge operations by the screw, a predetermined amount of the molding material can be injected into the mold unit held in the closed position while keeping the molding material in a molten state. Incidentally, the temperature of the molds of the mold unit 1 is preliminarily maintained at about 110.degree. C. upon the injection.

After the molding material is injected from the injection unit 22 into 2 sets of cavities of the mold unit 1, the obtained molded product is subjected to primary cooling in the mold unit 1. The time required for the primary cooling after the injection may be determined according to volume or surface area of the molded product and mold temperature. For example, when the molded product is produced from the above-mentioned molding material, the primary cooling time is about 20 to about 30 seconds. Further, in the mold unit 1, the molded product can be magnetized by permanent magnets disposed so as to surround each cavity, during the primary cooling, thereby obtaining a magnet roll.

Next, the magnet roll (molded product) is removed from the mold unit 1 by 2 sets of chucks 35 as a holding means, which are arranged on one of 2 sets of the arms 34. The thus removed magnet roll is subjected to secondary cooling while being held by the chucks 35. Incidentally, upon the secondary cooling, the temperature of the blocks 35c of the chuck 35 may be preliminarily adjusted to about 70.degree. C. to about 90.degree. C. by the heating medium. More specifically, the temperature of such chucks 35 is controlled such that the difference in temperature between the chucks 35 and the mold unit 1 falls in the range of 0 to 50.degree. C.

Specified operations for removal of the molded product are as follows. That is, when the mold unit 1 is opened, the chucks 35 disposed thereabove in a stand-by state is lowered and advanced to the region defined between the opened molds by operations of the first linear guide 32, the second linear guide 33 and the arms 34 and rotational operation of the chucks 35. By these operations, a pair of blocks 35c of each chuck 35 which has been preliminarily kept in an opened state, are respectively positioned on opposite sides of the magnet roll projected into the region defined between the opened molds. The pair of blocks 35c of each chuck 35 are caused to approach one another by the operation of the cylinder unit, so that the magnet roll is grasped therebetween.

The chucks 35 grasping the magnet roll is then moved back or retreated to the initial stand-by position. Since each block 35c of the chuck 35 is formed thereon with the grasping surface capable of contacting with the outer peripheral surface of the magnet roll and provided therein with a circulating path for heating medium, the magnet roll grasped by the chuck 35 can be effectively subjected to secondary cooling without generating internal strain therein.

On the other hand, after the molded magnet roll is removed by operating the chucks 35, the mold unit 1 is immediately closed and clamped, and the injection operation is carried out again in the same manner as described above. Similarly, after the molded product is subjected to the primary cooling in the mold unit, the obtained magnet roll is removed from the mold unit 1 by using the chucks 35 or the like and then subjected to the secondary cooling while being held by the chucks 35.

That is, in the apparatus according to the present invention, by controlling the ratio S2/S1 between the number of the chuck 35 and the number of cavity in the mold unit 1, and the ratio T2/T1 between the operation times of the mold unit 1 and each chuck 35, so as to establish the above-specified relationship therebetween, it becomes possible to continuously conduct the in-mold operations including a clamping step, an injecting and dwelling step, a primary cooling step, a mold-opening step and removing step of molded product from the mold, and further reduce the time required for cooling the molded product. In other words, in accordance with the present invention, an idling time (dead time) of the mold unit 1 can be effectively eliminated, and a sufficient time for cooling the magnet roll (molded product) in the chucks 35 can be assured. Therefore, by using the apparatus according to the present invention, it is possible to effectively produce electronic parts such as magnet rolls with a high dimensional accuracy without deformation thereof.

As described above, in the process according to the present invention, the molding material comprising a thermoplastic resin and an inorganic filler is injected from the injection machine 2 into cavity (or cavities) of the mold unit 1 to form a molded product, followed by subjecting the molded product to primary cooling in the mold unit 1. Thereafter, the obtained molded product is removed from the mold unit 1 using the chucks 35 as a holding means and then subjected to secondary cooling while being held by the chucks 35. In such a process of the present invention, by setting the ratio of the number of the chuck 35 to the number of the cavity of the mild unit 1 to a value not less than the ratio of the operation time of each chuck 35 to the operation time of the mold unit 1, it becomes possible to effectively produce electronic parts such as magnet rolls with a high dimensional accuracy without deformation thereof.

Also, in the injection-molding process according to the present invention, there is used the injection machine 2 comprising the kneader 21 and the injection unit 22. The molding material is melted and kneaded in the kneader 21, and the obtained kneaded material is injected from the injection unit 22 into cavity (or cavities) of the mold unit 1 while keeping the kneaded material in a molten state, thereby more effectively conducting the injection-molding process. Further, when the molded product is removed from the mold unit 1, the difference between the temperature of the mold unit 1 and the temperature of the chucks 35 is controlled to 0 to 50.degree. C. by passing the heating medium through the circulating path in the chucks 35, thereby producing such a molded product having much less internal strain.

Meanwhile, in the present invention, the number of the cavity in the mold unit 1 is not limited to two, but one cavity or not less than three cavities may be provided, as far as the number of the chuck 35 can satisfy the above-specified relationship.

As described above, in accordance with the present invention, when a molding material comprising a thermoplastic resin and an inorganic filler is subjected to injection-molding to form a molded product, the ratio of the number of holding means to the number of the cavity of the mold unit is set to the specified value to reduce an idling time of the mold unit. Accordingly, it becomes possible to reduce costs for production facilities and shorten the injection-molding cycle time, resulting in increased productivity. Further, the molded product which has been subjected to primary cooling in the mold unit is grasped by the holding means and removed from the mold unit, and then subjected to secondary cooling for a sufficient period of time while being held by the holding means, thereby preventing occurrence of internal strain in the molded product even after molded, and effectively preventing deformation of the molded product. Accordingly, the present invention is usefully applied to the production of electronic parts such as magnet rolls which are required to have a high dimensional accuracy.

EXAMPLES

The present invention will be described in more detail by Example, but the Example is not intended to limit the scope of the present invention.

The degree of deformation (degree of warpage or bend) of a molded product was measured in the following manner. After an outer diameter of the molded product was measured, the molded product was rotated in parallel laser beam to measure a maximum rotational outer diameter thereof. The difference between the maximum rotational outer diameter and the static outer diameter of the molded product was calculated and determined as the degree of deformation thereof. In the present invention, it is preferred that the degree of deformation (difference) of the molded product be not more than 100 .mu.m.

Example 1

Using the injection-molding apparatus shown in FIG. 1, 89 parts by weight (89.0% by weight) of magnetic particles prepared by treating bond magnet ferrite particles "MA95I" (produced by TODA KOGYO CORP.) with 0.5 part by weight of a silane coupling agent "A-1120" (produced by NIPPON UNICAR CO., LTD.) was mixed with 11 parts by weight (10.9% by weight) of nylon-6 particles "P101F" (produced by UBE KOSAN CO., LTD.) as a thermoplastic resin, and 0.1 part by weight (0.1% by weight) of a metal salt of stearic acid as a lubricant. The mixture was kneaded at a resin temperature of 290.degree. C. using a KCK kneader ("100-35VEX-6", manufactured by KCK CORP.) as the kneader 21. Next, using an injection-molding machine ("140-ton model", manufactured by NISSEI RESIN CO., LTD.), the kneaded material was injected into a mold having two cavities, in which the temperature thereof is maintained at 110.degree. C., thereby obtaining a cylindrical molded product having a diameter of about 0.96 cm and a length of about 22 cm. As the mold, there was used such a mold into which a plural of permanent magnets was incorporated along the longitudinal direction thereof such that a plural of magnetic poles was formed along the longitudinal direction of the molded product.

The respective operation times in the mold unit 1 during the injection-molding process were as follows:

clamping step (t1): about 2 seconds;

injecting/dwelling step (t2): about 6 seconds;

in-mold cooling step (primary cooling step) (t3): about 25 seconds;

mold-opening step (t4): about 2 seconds; and

removing step of the molded product (t5): about 6 seconds.

The first total operation time (first molding cycle time:T1) was about 41 seconds.

The molded product was grasped by the first chucks 35 made of aluminum and maintained at 80.degree. C. (difference between the temperature of the chucks 35 and that of the mold unit 1 was 30.degree. C.), and removed from the mold unit 1. Next, by being allowed to stand at a room temperature or gradually decreasing the temperature of heating medium circulated through the chucks 35, the grasped molded product was cooled for about 72 seconds (operation time of the first chucks 35:T2), thereby obtaining a magnet roll.

On the other hand, in the mold unit from which the molded product was already removed by the first chucks 35, the second injection-molding operation including a clamping step, an injecting/dwelling step, an in-mold cooling (primary cooling) step, a mold-opening step and a removing step of molded product from the mold was conducted for the same operation time as that of the first operation. Next, the obtained molded product was grasped by the second chucks 35 and removed from the mold unit 1. Further, the molded product grasped by the second chucks 35 was cooled in the same manner as described above with respect to the first chucks 35, thereby obtain a magnet roll.

Successively, in the mold unit 1 from which the molded product was already removed by the second chucks 35, the third injection-molding operation including a clamping step, an injecting/dwelling step, an in-mold cooling (primary cooling) step, a mold-opening step and a removing step of molded product from the mold was conducted for the same operation time as those of the first or second operations. Next, the molded product was grasped by the first chucks 35 which was already kept in a stand-by position (stand-by time (T3): about 10 seconds) after completion of cooling the molded product obtained in the first injection-molding operation, and then the molded product was cooled while being held by the first chucks 35, thereby obtaining a magnet roll. An average degree of deformation of the thus obtained 20 magnet rolls was 78 .mu.m.

CLM What is claimed is:

1. A method for injection-molding a molding material, which method comprises: (a) injecting a molding material comprising a thermoplastic resin and in inorganic filler from an injection unit into a cavity of a mold unit to form a molded product; (b) subjecting said molded product to a primary cooling in said cavity; (c) removing said molded product from said mold unit using chucks as a holding means while circulating a heating medium through said chucks to control a difference between a temperature of said mold unit and a temperature of said holding means to 0 to 50.degree. C.; and (d) subjecting said molded product to a secondary cooling while holding said molded product by said chucks, wherein the ratio of the number of said chucks to the number of said cavities is set to a value not less than a ratio of an operation time of each chuck to an operation time of said mold unit.

2. A method according to claim 1, wherein said injection machine comprises a kneader for melting and kneading a molding material for said molded product, and an injection unit for injecting the kneaded material into said cavities while maintaining said kneaded material in a molten state.

3. A method according to claim 1, wherein said molding material for the molded product comprises at least one thermoplastic resin selected from the group consisting of a polyamide resin, a polyphenylene sulfide resin, an ethylene-ethyl acrylate resin, an ethylene-ethyl methacrylate resin, a liquid crystalline polymer and a chlorinated polyethylene resin, and at least one inorganic filler selected from the group consisting of ferrite particles, iron oxide particles and metal particles.

4. A method according to claim 3, wherein said molded product is a substantially bar-shaped magnet roll.

5. An injection-molding apparatus comprising: an injection machine; a mold unit connected to said injection machine and comprising separable molds, which constitutes therein a cavity for forming a molded product; and a holding means disposed adjacent to said mold unit for removing said molded product from said mold unit, comprising a plurality of chucks adapted to advance into and retreat from a region defined between the opened molds of the mold unit, said molded product being subjected to a primary cooling in the cavity of said mold unit and then subjected to a secondary cooling after removal from the mold unit, the ratio of

the number of said chucks to the number of said cavities being set to a value not less than a ratio of an operation time of each chuck to an operation time of said mold unit, each of said chucks comprising a pair of blocks being opposed to each other and each having a grasping surface which can be brought into a face contact with an outer peripheral surface of said molded product, and each of said blocks being provided therein with a circulating path through which a heating medium is passed to cool said grasping surface.

6. An injection-molding apparatus according to claim 5, wherein said injection machine comprises a kneader for melting and kneading a molding material for said molded product, and an injection unit for injecting the kneaded material into said cavities while maintaining said material in a molten state.

7. An injection-molding apparatus according to claim 5, wherein said molding material for the molded product comprises at least one thermoplastic resin selected from the group consisting of a polyamide resin, a polyphenylene sulfide resin, an ethylene-ethyl acrylate resin, an ethylene-ethyl methacrylate resin, a liquid crystalline polymer and a chlorinated polyethylene resin, and at least one inorganic filler selected from the group consisting of ferrite particles, iron oxide particles and metal particles.

8. An injection-molding apparatus according to claim 7, wherein said molded product is a substantially bar-shaped magnet roll.

9. An injection-molding apparatus comprising: an injection machine; a mold unit connected to said injection machine and comprising separable molds, which constitutes therein a cavity for forming a molded product; and a holding means disposed adjacent to said mold unit for removing said molded product from said mold unit, comprising a plurality of chucks adapted to advance into and retreat from a region defined between said molds of the mold unit, said molded product being subjected to a primary cooling in the cavity of said mold unit held in a closed position and then to a secondary cooling after removal from the mold unit, to form a substantially bar-shaped magnet roll comprising a thermoplastic resin and an inorganic filler, the ratio of the number of said chucks to the number of the cavities being set to a value not less than a ratio of an operation time of each chuck to an operation time of said mold unit, each of said chucks comprising a pair of blocks being opposed to each other and each having a grasping surface which can be brought into a face contact with an outer peripheral surface of said molded product, and each of said blocks being provided therein with a circulating path through which a heating medium is passed to cool said grasping surface.

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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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